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File 351:DERWENT WPI 1981-1996/UD=9629;UA=9625;UM=9617
    (c)1996 Derwent Info Ltd

    Set  Items  Description
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?s soluble? and receptor? and (tnf? or (tumour or tumor)(w)necrosis(w)factor?)
        82211  SOLUBLE?
        12486  RECEPTOR?
          856  TNF?
         9419  TUMOUR
          414  TUMOR
         1412  NECROSIS
        61062  FACTOR?
          681  (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?
    S1     24  SOLUBLE? AND RECEPTOR? AND (TNF? OR (TUMOUR OR
              TUMOR)(W)NECROSIS(W)FACTOR?)
?s s1 not py=1992:1996pb
          24  S1
     2201410  PY=1992 : PY=1996PB
    S2     0  S1 NOT PY=1992:1996PB
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FILE 'USPAT' ENTERED AT 11:27:34 ON 02 AUG 96

(FILE 'USPAT' ENTERED AT 11:27:34 ON 02 AUG 96)

L1 336 S SOLUBLE? AND RECEPTOR? AND (TNF? OR (TUMOUR OR TUMOR)(W)
NEC
L2 336 S SOLUBLE AND (RECEPTOR OR RECEPTORS) AND (TNF? OR (TUMOUR
OR
L3 139 S L2 NOT FY>=1992
L4 14 S L3 AND (TNF?/TI OR TNF?/AB OR (TUMOUR OR TUMOR)(W)NECRO
SIS

=> d l4 cit ab fd 1-

1. 5,436,154, Jul. 25, 1995, Monoclonal antibodies against human **Tumor** **Necrosis** **Factor** .alpha.; Elena Barbanti, et al., 435/240.27; 424/133.1, 158.1; 530/387.1, 388.23, 388.24 [IMAGE AVAILABLE]

US PAT NO: 5,436,154 [IMAGE AVAILABLE] L4: 1 of 14

ABSTRACT:
A monoclonal antibody is provided which is able to neutralize both human **TNF** .alpha. and **TNF** .beta., or a binding fragment thereof. A stable hybridoma cell line and progeny thereof are also provided which secrete such a monoclonal antibody. The monoclonal antibody or a fragment thereof may be used to detect the content of human **TNF** in a sample of body fluid.
DATE FILED: Dec. 13, 1991

2. 5,422,104, Jun. 6, 1995, **TNF**-muteins; Walter Fiers, et al., 424/85.1; 435/69.5; 530/351 [IMAGE AVAILABLE]

US PAT NO: 5,422,104 [IMAGE AVAILABLE] L4: 2 of 14

ABSTRACT:
It is an object of this invention to provide a human **Tumor** **Necrosis** **Factor** mutein or a pharmaceutically acceptable salt thereof characterized in that the **TNF** sequence is changed by a deletion, insertion, substitution or combinations thereof, of one or more amino acids so that the mutein shows a significant difference between its binding affinity to the human p75-**Tumor**-**Necrosis**-**Factor**-**Receptor** and to the human p55-**Tumor**-**Necrosis**-**Factor**-**Receptor**. The invention also includes DNA sequences coding for such muteins, vectors comprising such DNA sequences, host cells transformed with such vectors and a process for the production of such muteins employing such transformed host cells and pharmaceutical compositions containing such muteins and their use for the treatment of illnesses, for example cancer.
DATE FILED: Nov. 20, 1991

3. 5,395,760, Mar. 7, 1995, DNA encoding **tumor** **necrosis** **factor**-.alpha. and -.beta. **receptors**; Craig A. Smith, et al., 435/240.1; 424/85.1; 435/69.4, 172.3; 530/351, 388.23; 536/23.51 [IMAGE AVAILABLE]

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L4: 3 of 14

ABSTRACT:
Tumor **necrosis** **factor** **receptor** proteins, DNAs and expression vectors encoding **TNF** **receptors**, and processes for producing **TNF** **receptors** as products of recombinant cell culture, are disclosed.
DATE FILED: May 10, 1990

4. 5,317,019, May 31, 1994, Inhibition of interleukin-1 and **tumor** **necrosis** **factor** production by monocytes and/or macrophages; Paul E. Bender, et al., 514/224.2, 230.5, 258, 303, 333, 338, 339 [IMAGE AVAILABLE]

US PAT NO: 5,317,019 [IMAGE AVAILABLE] L4: 4 of 14

ABSTRACT:

A method of inhibiting the production of interleukin-1 by monocytes and/or macrophages in a human in need thereof which comprises administering to such a human an effective, interleukin-1 production inhibiting amount of a diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead atom wherein said second ring may also contain sulfur, oxygen or an additional nitrogen atom, and may contain additional unsaturation.
This invention relates to a method of inhibiting the production of **Tumor** **Necrosis** **Factor** (**TNF**) by monocytes or macrophages in a human in need thereof which comprises administering to such mammal an effective, **TNF** production inhibiting amount of a compound of Formula (I) as described herein. The compounds of Formula (II) are generally described as diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead wherein said ring may also contain sulfur, oxygen, or an additional nitrogen atom, and may contain additional unsaturation.
DATE FILED: Dec. 12, 1991

5. 5,256,534, Oct. 26, 1993, CD4.sup.+, latently HIV-1-infected hematopoietic progenitor cells; Salvatore T. Butera, et al., 435/5, 7.24, 8, 239, 240.26 [IMAGE AVAILABLE]

US PAT NO: 5,256,534 [IMAGE AVAILABLE] L4: 5 of 14

ABSTRACT:
The present invention relates to a unique physiologic model of chronic human immunodeficiency virus type-1 (HIV-1) infection. In particular, the present invention relates to a chronically infected promyelocyte cell line harboring a single integrated provirus. Unlike other models of chronic infection, the cell line of the present invention remain CD4.sup.+ under normal culture conditions during which <10% of the cells constitutively express HIV-1 proteins. However, when treated with **tumor** **necrosis** **factor**-alpha (**TNF**-.alpha.), the cell line dramatically increased (>35-fold) HIV-1 expression and rapidly down-modulated surface CD4, as >95% of the cells became HIV-1.sup.+. These results with the new OM-10.1 cell line demonstrate that CD4 surface expression can be maintained during chronic infection and is critically dependent upon the state of viral activation; that CD4-gp160/120 intracellular complexing is responsible for CD4 down-modulation; and that protein kinase pathways function not only in the primary induction of latent HIV-1 but are also involved in maintaining the state of viral activation.
DATE FILED: Aug. 9, 1991

6. 5,223,395, Jun. 29, 1993, Immunometric assays for **tumor** **necrosis** **factor**-alpha and methods for preventing the loss of biological activity of **tumor** **necrosis** **factor**-alpha in biological samples; Eva J. Gero, 435/7.1, 7.94, 240.27; 436/548; 530/351, 388.23 [IMAGE AVAILABLE]

US PAT NO: 5,223,395 [IMAGE AVAILABLE] L4: 6 of 14

ABSTRACT:
An immunometric assay is disclosed for biologically active **tumor** **necrosis** **factor** in a biological sample comprising, forming a complex of a first labeled monoclonal antibody, biologically active **TNF**, and a second monoclonal antibody which can be bound to an insoluble substrate and detecting the amount of label associated with the complex. The assay is characterized by employing first and second monoclonal antibodies which react with the same epitopic site on **TNF**-alpha monomer. A method is also disclosed for blocking accelerated **TNF** degradation in a non-preserved biological sample, such as blood, comprising contacting the biological sample with EDTA, luminol, or a combination thereof.
DATE FILED: Dec. 1, 1988

7. 5,206,345, Apr. 27, 1993, IL-4 and **TNF** induce mAb 6G10-recognized expression on bone marrow stromal cells; Boris Masinovsky, et al., 530/388.7; 435/7.21, 240.27; 436/548 [IMAGE AVAILABLE]

US PAT NO: 5,206,345 [IMAGE AVAILABLE] L4: 7 of 14

ABSTRACT:
An improved method of screening a cell line for the production of a binding partner that binds with a cell-surface molecule, by contacting the binding partner with IL4-activated and nonactivated human bone marrow stromal cells, and selecting binding partners that bind to the IL4-activated human bone marrow stromal cells but not to the nonactivated human bone marrow stromal cells. The selected binding partners may thereafter be tested for the ability to block CD34.sup.+ bone marrow cell binding to IL4-activated human bone marrow stromal cells. The binding partners are preferably also characterized by binding to human VCAM-1. A representative embodiment is mAb 6G10 produced by hybridoma ATTC No. HB 10519.
DATE FILED: Aug. 2, 1990

8. 5,166,137, Nov. 24, 1992, Guluronic acid polymers and use of same for inhibition of cytokine production; Marit Otterlei, et al., 514/23, 886, 887, 921 [IMAGE AVAILABLE]

US PAT NO: 5,166,137 [IMAGE AVAILABLE] L4: 8 of 14

ABSTRACT:
A family of compounds effective in inhibiting interleukin-1 (IL-1) production, interleukin-6 (IL-6), **tumor** **necrosis** **factor** (**TNF**) production, and the production of other leukocyte derived cytokines is comprised of oligomers and polymers of .alpha.1-4 linked L-guluronic acid residues which may be administered to a human or mammal in an amount sufficient to inhibit the production effect of leukocyte-derived cytokines. The inhibition of IL-1, IL-6 and **TNF**, and other cytokines in mammals is implicated in alleviation of a wide variety of disease conditions.
DATE FILED: Mar. 27, 1991

9. 5,098,702, Mar. 24, 1992, Combination therapy using interleukin-2 and **tumor** **necrosis** **factor**; Robert Zimmerman, et al., 424/85.1, 85.2; 514/2, 8 [IMAGE AVAILABLE]

US PAT NO: 5,098,702 [IMAGE AVAILABLE] L4: 9 of 14

ABSTRACT:
Anti-tumor activity in mammals can be augmented by administering to the mammalian host a synergistically effective amount of **TNF** and IL-2 or of **TNF** and IFN-.beta., or of **TNF**, IL-2 and IFN-.beta. in combination. The composition of **TNF** and IL-2 and/or IFN-.beta. may be prepared in vitro or administered separately to the host. If the **TNF** and IL-2 are administered sequentially, the **TNF** must be administered prior to the IL-2 to obtain synergy. The composition is useful for treating such cancers as mastocytoma, melanoma, leukemia, lymphoma, mammary adenocarcinoma, and pharyngeal squamous cell carcinoma.
DATE FILED: Jun. 26, 1989

10. 4,985,241, Jan. 15, 1991, Therapeutic combination of free-radical scavenger and **tumor** **necrosis** **factor**; Robert Zimmerman, et al., 424/85.1, 85.2; 514/2, 8, 885 [IMAGE AVAILABLE]

US PAT NO: 4,985,241 [IMAGE AVAILABLE] L4: 10 of 14

ABSTRACT:
Damage to cells, tissue and other body parts in a mammalian host may be treated by using a lymphokine or cytotoxin in conjunction with at least one biological modifier, which may be a free radical scavenger or a metabolic inhibitor. The lymphokine or cytotoxin is preferably **tumor** **necrosis** **factor** and the biological modifier is preferably uric acid, buthionine sulphoximine, vitamin C, aspirin, or nordihydroguaiaretic acid. Such a combination may be used to treat, for example, cancer, infectious diseases, and damage caused by radiation therapy, high oxygen tension, and chemotherapy.
DATE FILED: Aug. 25, 1989

11. 4,963,354, Oct. 16, 1990, Use of **tumor** **necrosis** **factor** (**TNF**) as an adjuvant; H. Michael Shepard, et al., 424/85.1, 85.4;

514/2, 8, 12, 21, 885 [IMAGE AVAILABLE]

US PAT NO: 4,963,354 [IMAGE AVAILABLE] L4: 11 of 14

ABSTRACT:
Tumor **necrosis** **factors**, alone or together with cytokines such as IL-1 or INF-.gamma., are capable of serving as non-toxic vaccine adjuvants.
DATE FILED: Jan. 21, 1987

12. 4,863,727, Sep. 5, 1989, Combination therapy using interleukin-2 and **tumor** **necrosis** **factor**; Robert Zimmerman, et al., 424/85.2; 435/69.5, 69.52; 514/2, 8 [IMAGE AVAILABLE]

US PAT NO: 4,863,727 [IMAGE AVAILABLE] L4: 12 of 14

ABSTRACT:
Anti-tumor activity in mammals can be augmented by administering to the mammalian host a synergistically effective amount of **TNF** and IL-2 or of **TNF** and IFN-.beta., or of **TNF**, IL-2 and IFN-.beta. in combination. The composition of **TNF** and IL-2 and/or IFN-.beta. may be prepared in vitro or administered separately to the host. If the **TNF** and IL-2 are administered sequentially, the **TNF** must be administered prior to the IL-2 to obtain synergy. The composition is useful for treating such cancers as mastocytoma, melanoma, leukemia, lymphoma, mammary adenocarcinoma, and pharyngeal squamous cell carcinoma.
DATE FILED: Nov. 16, 1988

13. 4,857,314, Aug. 15, 1989, C-reactive proteins in treatment of animal and human cancers; Timothy E. O'Connor, et al., 424/85.1; 514/2, 8, 21, 885, 886; 530/351 [IMAGE AVAILABLE]

US PAT NO: 4,857,314 [IMAGE AVAILABLE] L4: 13 of 14

ABSTRACT:
A pharmaceutical composition comprising an effective antitumor amount of a protein having tumor necrosis activity such as human **tumor** **necrosis** **factor** and an effective immune system stimulating amount of C-Reactive Protein to enhance the antitumor activity of the **tumor** **necrosis** **factor** and a method for treating tumors which comprises administering to a subject having a tumor an effective antitumor amount of a protein having tumor necrosis activity and an effective amount of C-Reactive Protein to stimulate the immune system of the subject thereby enhancing the antitumor activity of the protein.
DATE FILED: Jul. 18, 1986

14. 4,650,674, Mar. 17, 1987, Synergistic cytotoxic composition; Bharat B. Aggarwal, et al., 424/85.5, 85.4; 435/69.5; 514/12; 930/143, 144 [IMAGE AVAILABLE]

US PAT NO: 4,650,674 [IMAGE AVAILABLE] L4: 14 of 14

ABSTRACT:
Compositions comprising an interferon and a cytotoxic protein designated **tumor** **necrosis** **factor** exhibit a synergistic cytotoxic effect on tumor cells.
DATE FILED: Dec. 3, 1984

Set Items Description
S1 7300 (TNF? OR (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?) AND (ANTAGONIST? OR ANTIBOD? OR BINDING(W)PROTEIN? OR SOLUBLE(W)RECEPTOR?)
S2 2224 S1 NOT PY>=1992
S3 1104 S2 AND (TREAT? OR THERAP? OR PATIENT?)
S4 36 S3 AND ARTHRITIS
S5 25 S3 AND RHEUMATOID(W)ARTHRITIS
S6 36 S4 OR S5
?□s6/3,ab/all

6/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

08042467 92180467
[The role of cytokines and growth factors in rheumatoid joint destruction]
Die Rolle von Zytokinen und Wachstumsfaktoren bei der rheumatoiden Gelenkdestruktion.
Alsalameh S; Kalden JR; Burmester GR
Institut fur Klinische Immunologie und Rheumatologie, Universitat Erlangen-Nurnberg.
Z Rheumatol (GERMANY) Nov-Dec 1991, 50 (6) p347-59, ISSN 0340-1855
Journal Code: Y0V
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English
Abstract
Cytokines and growth factors are important mediators of inflammation and play a major role in both the physiological regulation of bone and cartilage metabolism, and in the destruction of joint-related structures. These complex biological regulatory events have to be regarded as net effects which are dependent on the individual actions of the different cytokines and their corresponding inhibitors in the pericellular environment of the cells present in the inflamed tissues. These effects can be antagonized on various levels by natural or artificial inhibitory molecules. The determination and characterization of cytokines and their inhibitors in body fluids and tissues may contribute to a better understanding of the basic mechanisms of the pathogenesis of inflammatory joint diseases, and may help to develop better modalities of **therapy**. The objective of the present review is to outline important actions of selected cytokines and growth factors on cells and the surrounding matrix of bone and cartilage in **rheumatoid** **arthritis**. It will focus on interleukin-1 (IL-1), IL-1 inhibitors, **Tumor**-**Necrosis**-**Factor** -alpha (**TNF**-alpha), **TNF** inhibitors, Interleukin-6 (IL-6), colony-stimulating factors (CSF's), Interferon-gamma (IFN-gamma), growth factors, eicosanoids and prostaglandins, all of which are important in the effector phase of tissue destruction.

6/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

07997760 92135760
Cooperation between **tumor** **necrosis** **factor** (**TNF**) and platelet-activating factor (PAF) in the inflammatory response.
Maestre C; Zarco P; Gomez-Guerrero C; Gonzalez E; Herrero-Beaumont G; Braquet M; Egido J
Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Spain.
J Lipid Mediat (NETHERLANDS) 1990, 2 Suppl pS151-9, ISSN 0921-8319
Journal Code: A6K
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this paper we have examined the cooperation between **TNF** and PAF in the generation of superoxide anion (O2-) in vitro by polymorphonuclear cells (PMNs), as well as their ability to induce joint inflammation when injected into the knee of healthy rabbits. **TNF** and PAF directly stimulated the generation of a small amount of O2- by PMNs. **TNF** pretreatment of PMNs induced a certain synergy in the O2- production, when these cells were later stimulated with PAF. When PAF receptor **antagonists** were added, the O2- release was inhibited. The injection of

either **TNF** or PAF into the knee joint of normal rabbits induced a dose-dependent accumulation of leukocytes in the synovial cavity 24 h after administration. When **TNF** was administered 1 h before PAF, a synergistic response in the accumulation of leukocytes in the joint fluid was noted. The administration of BN 52726 by the intraperitoneal route markedly inhibited the cell accumulation induced by **TNF** and PAF. Histological signs of inflammation were noted in the synovial lining of joints injected with **TNF** and PAF. These results suggest that **TNF** can amplify the inflammatory response induced by PAF. PAF **antagonists** can inhibit this effect and thus may be of **therapeutic** value in different pathological situations.

6/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

07959520 92097520
Transgenic mice expressing human **tumour** **necrosis** **factor**: a predictive genetic model of **arthritis**.
Keffer J; Probert L; Cazlaris H; Georgopoulos S; Kaslaris E; Kioussis D; Kollias G
Laboratory of Molecular Genetics, Hellenic Pasteur Institute, Athens, Greece.
EMBO J (ENGLAND) Dec 1991, 10 (13) p4025-31, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have generated transgenic mouse lines carrying and expressing wild-type and 3'-modified human **tumour** **necrosis** **factor** (hTNF-alpha, cachectin) transgenes. We show that correct, endotoxin-responsive and macrophage-specific hTNF gene expression can be established in transgenic mice and we present evidence that the 3'-region of the hTNF gene may be involved in macrophage-specific transcription. Transgenic mice carrying 3'-modified hTNF transgenes shows deregulated patterns of expression and interestingly develop chronic inflammatory polyarthritis. **Treatment** of these arthritic mice with a monoclonal **antibody** against human **TNF** completely prevents development of this disease. Our results indicate a direct involvement of **TNF** in the pathogenesis of **arthritis**. Transgenic mice which predictably develop **arthritis** represent a novel genetic model by which the pathogenesis and **treatment** of this disease in humans may be further investigated.

6/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

07916586 92054586
Structures of free and inhibited human secretory phospholipase A2 from inflammatory exudate.
Scott DL; White SP; Browning JL; Rosa JJ; Gelb MH; Sigler PB
Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06511.
Science (UNITED STATES) Nov 15 1991, 254 (5034) p1007-10, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: GM22324, GM, NIGMS; HL36235, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Phospholipase A2 (PLA2) participates in a wide range of cellular processes including inflammation and transmembrane signaling. A human nonpancreatic secretory PLA2 (hnps-PLA2) has been identified that is found in high concentrations in the synovial fluid of **patients** with **rheumatoid** **arthritis** and in the plasma of **patients** with septic shock. This enzyme is secreted from certain cell types in response to the proinflammatory cytokines, **tumor** **necrosis** **factor** or interleukin-1. The crystal structures of the calcium-bound form of this enzyme have been determined at physiological pH both in the presence [2.1 angstrom (A) resolution] and absence (2.2 A resolution) of a transition-state analogue. Although the critical features that suggest the chemistry of catalysis are identical to those inferred from the crystal structures of other extracellular PLA2s, the shape of the hydrophobic

channel of hnps-PLA2 is uniquely modulated by substrate binding.

6/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

07891123 92029123
Localization of **tumor** **necrosis** **factor** alpha in synovial tissues and at the cartilage-pannus junction in **patients** with **rheumatoid** **arthritis**.
Chu CQ; Field M; Feldmann M; Maini RN
Division of Clinical Immunology, Mathilda and Terence Kennedy Institute of Rheumatology, Hammersmith, London, England.
Arthritis Rheum (UNITED STATES) Sep 1991, 34 (9) p1125-32, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using immunoaffinity-purified polyclonal anti-human recombinant **tumor** **necrosis** **factor** alpha (**TNF** alpha) F(ab')2 fragments and immunohistochemical techniques, the cells that make **TNF** alpha were localized in the inflamed synovial tissue of **patients** with **rheumatoid** **arthritis** (RA) and osteoarthritis (OA). Anti-**TNF** alpha **antibody**-stained cells were demonstrated in 9 of 11 RA and 2 of 4 OA but none of 5 normal synovial membranes examined. In RA, 26-64% of the lining layer cells were positive for **TNF** alpha. In the interaggregate area, 10-30% of the cells contained **TNF** alpha, often in a perivascular distribution, and up to 19% of the cells in lymphoid aggregates stained for **TNF** alpha. Some endothelial cells also stained with these **antibodies**. In OA tissues, the **TNF** alpha-containing cells were found predominantly in the deeper layer. Cells containing **TNF** alpha were also found at the cartilage-pannus junction in all 4 RA specimens examined. Double immunofluorescence analysis demonstrated that most **TNF** alpha-secreting cells in the RA synovial membrane expressed the monocyte/macrophage marker antigens CD11b and CD14, and a few expressed the T cell marker CD3. Our findings provide histologic evidence that **TNF** alpha is locally produced in the lining and deeper layers of the synovium by cells of the monocyte/macrophage lineage, supporting its role in inflammation. Further, our findings demonstrate that **TNF** alpha is produced by cells at the cartilage-pannus junction, which could affect chondrocyte metabolism, leading to the cartilage degradation in RA.

6/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

07875203 92013203
A human renal cancer line as a new antigen source for the detection of **antibodies** to cytoplasmic and nuclear antigens in sera of **patients** with Wegener's granulomatosis.
Mayet WJ; Hermann E; Csernok E; Knuth A; Poralla T; Gross WL; Meyer zum Buschenfelde KH
I. Medizinische Klinik, Universitat Mainz, F.R.G.
J Immunol Methods (NETHERLANDS) Sep 20 1991, 143 (1) p57-68, ISSN 0022-1759 Journal Code: IFE
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Autoantibodies directed against cytoplasmic antigens of neutrophils (ANCA), especially proteinase 3 (C-ANCA), have proved to be a useful clinical tool to support the diagnosis or to monitor disease activity in Wegener's granulomatosis (WG). Till now, human neutrophil granulocytes have represented the major antigen source used to detect **antibodies** in WG by the immunofluorescence technique (IFT). We have tested serum samples of 164 **patients** with different connective tissue diseases (50 suffering from clinically active WG) performing IFT on a human renal cancer line (SK-RC11) and have found **antibodies** against the nuclear and cytoplasmic antigens in 39 **patients**. C-ANCA+ sera displayed a characteristic diffuse cytoplasmic staining pattern. **Antibody** titers measured with human granulocytes were comparable to titers obtained using culture cells. **Antibody** binding could be inhibited by preabsorption with an extract of human granulocytes or purified proteinase 3. A protein of 29 kDa MW could

be isolated by affinity purification using a SK-RC11 extract and a high-titer C-ANCA+ serum and antigenic identity was further confirmed by IFT using a monoclonal **antibody** to proteinase 3. **Treatment** of tumor cells with cytokines (interferon, **tumor** **necrosis** **factor**) led to a time dependent translocation of the antigen into the nucleus and back to the cytoplasm. The antigen was also expressed on the surface of live cells colocalized with MHC II. In addition, 21 WG **patients** had **antibodies** to cytoplasmic organelles identified by laser scanning microscopy as secretory vesicles of the Golgi complex, and five had **antibodies** to nuclear antigens. This is, to the best of our knowledge, the first report of proteinase 3 in human non-leukemic cells. Our data demonstrate, that the repertoire of antigens recognized by **antibodies** in WG sera is not limited to human neutrophils and monocytes and indicates a possible functional role of the antigenic proteins.

6/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

07875008 92013008
Synovial tissue macrophage as a source of the chemotactic cytokine IL-8.
Koch AE; Kunkel SL; Burrows JC; Evanoff HL; Haines GK; Pope RM; Strieter RM
Department of Medicine, Northwestern University Medical School, Chicago, IL 60611.
J Immunol (UNITED STATES) Oct 1 1991, 147 (7) p2187-95, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AR30692, AR, NIAMS; HL02401, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cells of the synovial microenvironment may recruit neutrophils (PMN) and lymphocytes into synovial fluid, as well as lymphocytes into the synovial tissues, of arthritic **patients**. We have investigated the production of the chemotactic cytokine IL-8 by using sera, synovial fluid, synovial tissue, and macrophages and fibroblasts isolated from synovial tissues from 75 arthritic **patients**. IL-8 levels were higher in synovial fluid from rheumatoid (RA) **patients** (mean +/- SE, 14.37 +/- 5.8 ng/ml), compared with synovial fluid from osteoarthritis **patients** (0.135 +/- 17 ng/ml) (p less than 0.05) or from **patients** with other arthritides (5.52 +/- 5.11 ng/ml). IL-8 from RA sera was 8.44 +/- 2.33 ng/ml, compared with nondetectable levels found in normal sera. IL-8 levels from RA sera and synovial fluid were strongly positively correlated (r = 0.96, p less than 0.05). Moreover, RA synovial fluid chemotactic activity for PMN in these fluids was inhibited 40 +/- 5% upon incubation with neutralizing polyclonal **antibody** to IL-8. Synovial tissue fibroblasts released only small amounts of constitutive IL-8 but could be induced to produce IL-8 by stimulation with either IL-1 beta, **TNF**-alpha, or LPS. In contrast, unlike normal PBMC or alveolar macrophages, macrophages isolated from RA synovial tissue constitutively expressed both IL-8 mRNA and antigenic IL-8. RA synovial macrophage IL-8 expression was not augmented by incubation with either LPS, **TNF** -alpha, or IL-1 beta. Immunohistochemical analysis of synovial tissue showed that a greater percentage of RA macrophages than osteoarthritis macrophages reacted with anti-IL-8. Whereas macrophages were the predominant cell for immunolocalization of IL-8, less than 5% of synovial tissue fibroblasts were positive for immunolocalized IL-8. These results suggest that macrophage-derived IL-8 may play an important role in the recruitment of PMN in synovial inflammation associated with RA.

6/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

07868267 92006267
Identification of the major fibroblast growth factors released spontaneously in inflammatory **arthritis** as platelet derived growth factor and **tumour** **necrosis** **factor**-alpha.
Thornton SC; Por SB; Penny R; Richter M; Shelley L; Breit SN
Centre for Immunology, St Vincent's Hospital, Sydney, Australia.
Clin Exp Immunol (ENGLAND) Oct 1991, 86 (1) p79-86, ISSN 0009-9104 Journal Code: DD7

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Rheumatoid **arthritis** is characterized by chronic inflammation and proliferation of a number of important elements within the joint including the synovial fibroblasts. Elevated levels of a number of cytokines such as Il-1, IL-2, IL-6, interferon-gamma (IFN-gamma), transforming growth factor-beta and **tumour** **necrosis** **factor**-alpha (**TNF**-alpha) have been detected in the synovial fluid of **patients** with **rheumatoid** **arthritis** and other inflammatory arthritides. It seems likely that local release of such mediators may be responsible for the proliferation and overgrowth of connective tissue elements in these disorders. In order to ascertain whether there was evidence to suggest local production or release of fibroblast growth factors in the joint in inflammatory **arthritis** , and to determine their identity, cells were obtained from the synovial fluid of 15 **patients** with chronic inflammatory arthritides. All subjects' synovial fluid cells spontaneously released growth factor activity for fibroblasts. This was present in large amounts, being detectable in culture supernatants diluted to a titre of at least 1/625. By a series of depletion experiments using solid-phase bound **antibodies** to cytokines, it was possible to demonstrate that this activity was due to **TNF** -alpha and platelet-derived growth factor (PDGF). Thus, this study showed for the first time that functionally active PDGF was released from synovial fluid cells. Both PDGF and **TNF**-alpha appeared to contribute in approximately equal amounts to this fibroblast growth factor activity, and were synergistic in effect. Thus this study provides evidence for the local production and release of these two cytokines and suggests that together they are the dominant factors in fibroblast proliferation within the synovial cavity.

6/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

07836652 91355652
Elevated levels of circulating **tumor** **necrosis** **factor**-alpha, interferon-gamma, and interleukin-2 in systemic reactions induced by anti-CD4 **therapy** in **patients** with **rheumatoid** **arthritis** [letter]
Horneff G; Krause A; Emmrich F; Kalden JR; Burmester GR
Cytokine (UNITED STATES) May 1991, 3 (3) p266-7, ISSN 1043-4666 Journal Code: A52
Languages: ENGLISH
Document type: LETTER

6/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

07778488 91297488
Prolactin, immunoregulation, and autoimmune diseases.
Jara LJ; Lavalle C; Fraga A; Gomez-Sanchez C; Silveira LH; Martinez-Osuna P; Germain BF; Espinoza LR
Department of Internal Medicine, University of South Florida College of Medicine, Tampa.
Semin Arthritis Rheum (UNITED STATES) Apr 1991, 20 (5) p273-84, ISSN 0049-0172 Journal Code: UMV
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Cells of the immune system synthesize prolactin and express mRNA and receptors for that hormone. Interleukin 1, interleukin 6, gamma interferon, **tumor** **necrosis** **factor**, platelet activator factor, and substance P participate in the release of prolactin. This hormone is involved in the pathogenesis of adjuvant **arthritis** and restores immunocompetence in experimental models. In vitro studies suggest that lymphocytes are an important target tissue for circulating prolactin. Prolactin **antibodies** inhibit lymphocyte proliferation. Prolactin is comitogenic with concanavalin A and induces interleukin 2 receptors on the surface of lymphocytes. Prolactin stimulates ornithine. decarboxylase and activates protein kinase C, which are pivotal enzymes in the differentiation, proliferation, and function of lymphocytes. Cyclosporine A interferes with

prolactin binding to its receptors on lymphocytes. Hyperprolactinemia has been found in **patients** with systemic lupus erythematosus. Fibromyalgia, **rheumatoid** **arthritis**, and low back pain **patients** present a hyperprolactinemic response to thyrotropin-releasing hormone. Experimental autoimmune uveitis, as well as **patients** with uveitis whether or not associated with spondyloarthropathies, and **patients** with psoriatic **arthritis** may respond to bromocriptine **treatment**. Suppression of circulating prolactin by bromocriptine appears to improve the immunosuppressive effect of cyclosporine A with significantly less toxicity. Prolactin may also be a new marker of rejection in heart-transplant **patients**. This body of evidence may have an impact in the study of rheumatic disorders, especially connective tissue diseases. A role for prolactin in autoimmune diseases remains to be demonstrated.

6/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

07679491 91198491
Interleukin-1 and interleukin-1 antagonism.
Dinarello CA
Department of Medicine, Tufts University School of Medicine, Boston, MA.
Blood (UNITED STATES) Apr 15 1991, 77 (8) p1627-52, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: AI 15614, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
The polypeptide cytokine interleukin-1 (IL-1) affects nearly every tissue and organ system. IL-1 is the prototype of the pro-inflammatory cytokines in that it induces the expression of a variety of genes and the synthesis of several proteins that, in turn, induce acute and chronic inflammatory changes. IL-1 is also the prototypic "alarm" cytokine in that it brings about increases in a variety of defense mechanisms, particularly immunologic and hematologic responses. Most studies on the biology of IL-1 have been performed in animals, but human subjects have recently been injected with recombinant IL-1 and the results confirm the two fundamental properties of IL-1 as being both a mediator of disease as well as of host defense. However, in either situation, over or continued production of IL-1 leads to debilitation of normal host functions; therefore, reduction of IL-1 synthesis or its effects becomes a target of **therapy** in many diseases. In this review, the structure; gene expression, synthesis, and secretion of IL-1 are described. In addition, the two IL-1 surface receptors, possible signal transduction mechanisms, various biologic activities, and production of IL-1 during disease states are discussed. Similarities and differences between IL-1, **tumor** **necrosis** **factor**, and IL-6 are presented. Although various agents for reducing the synthesis and/or for antagonizing the effects of IL-1 have been proposed, the recent cloning of a naturally occurring IL-1 receptor **antagonist** (IL-1ra) has opened new experimental and clinical approaches. The ability of this IL-1ra to block the triggering of IL-1 receptors in animals without agonist effects has reduced the severity of diseases such as hemodynamic shock, lethal sepsis, inflammatory bowel disease, experimental **arthritis**, and the spontaneous proliferation of human leukemic cells.

6/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

07671162 91190162
Activation of CD16+ effector cells by rheumatoid factor complex. Role of natural killer cells in **rheumatoid** **arthritis** [see comments]
Hendrich C; Kuipers JG; Kolanus W; Hammer M; Schmidt RE
Department of Clinical Immunology, Center of Medicine and Dermatology, Hannover Medical School, Germany.
Arthritis Rheum (UNITED STATES) Apr 1991, 34 (4) p423-31, ISSN 0004-3591 Journal Code: 90M
Comment in Arthritis Rheum 1992 Jan;35(1):128
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The role of natural killer (NK) cells in **rheumatoid** **arthritis** (RA) remains unclear. A pathogenetic function of rheumatoid factors (RF) also has not been defined. In the present studies, natural killer (NK) cells were examined as a model for FC gamma receptor type III-positive (FC gamma RIII+) cells, with regard to their interaction with RF. NK cell antigen CD16 (FC gamma RIII) and CD56 expression and functional NK and **antibody** -dependent cell-mediated cytotoxicity (ADCC) activity were compared in peripheral blood lymphocytes and autologous synovial fluid lymphocytes (SFL) of RA **patients**. Peripheral blood lymphocytes and SFL showed normal CD56 expression. In contrast, both the frequency and the density of CD16 antigen were decreased in SFL. Furthermore, diminished NK cytotoxicity and a significant decrease in ADCC were observed in SF NK cells. In subsequent in vitro studies with normal fresh NK cells, it was demonstrated that IgG-containing RF complexes from RA **patients** induced a modulation of FC gamma RIII structure from the NK cell surface, a decrease in NK activity, and a complete loss of ADCC. When purified RF was incubated with NK-enriched cell lines from RA **patients**, increased transcription and subsequent production of interferon-gamma and **tumor** **necrosis** **factor** alpha were observed. These data suggest a direct involvement of RF complexes in the pathogenetic process of chronic inflammation in RA.

6/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

07666621 91185621
Urate crystals stimulate production of **tumor** **necrosis** **factor** alpha from human blood monocytes and synovial cells. Cytokine mRNA and protein kinetics, and cellular distribution.
di Giovine FS; Malawista SE; Thornton E; Duff GW
University Department of Medicine, Northern General Hospital, Edinburgh, United Kingdom.
J Clin Invest (UNITED STATES) Apr 1991, 87 (4) p1375-81, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: AR-10493, AR, NIAMS; AR-07107, AR, NIAMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Crystals of monosodium urate (MSU) provide a dose-dependent stimulus for the production by human blood monocytes of **tumor** **necrosis** **factor** (**TNF**), a cytokine with proinflammatory properties; **TNF** activity was inhibited selectively by monoclonal **antibody** to **TNF** alpha. Biologically active cell-associated **TNF** activity peaked at 3 h and was exceeded at 6 h by extracellular activity, which peaked at 12-18 h. Comparable kinetics were observed with immunoreactive **TNF** alpha. **TNF** alpha mRNA accumulation in monocytes stimulated with MSU crystals appeared as a single peak at 2-4 h, kinetics compatible with rapid production of a short half-life transcript. In contrast, crystals of calcium pyrophosphate or of hydroxyapatite did not stimulate significant production of **TNF** or of message. Fresh tophaceous material from a **patient** with gout contained significant levels of **TNF** alpha and cells cultured from the tophus produced **TNF** alpha in vitro. In rheumatoid synovial cells, spontaneous release of **TNF** alpha was increased by in vitro exposure to MSU crystals. Taken together with earlier work, these results support an expanded view of gouty inflammation in which the crystal-stimulated production of cytokines provides a crucial link between crystal deposition and many of the clinical and pathological facts of both acute and chronic gouty **arthritis**.

6/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

07658525 91177525
Mechanisms of immune injury in **rheumatoid** **arthritis**: evidence for the involvement of T cells and heat-shock protein.
Strober S; Holoshitz J
Stanford University School of Medicine, Department of Medicine, CA 94305.
Immunol Rev (DENMARK) Dec 1990, 118 p233-55, ISSN 0105-2896 Journal Code: GG4

Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Evidence for the involvement of T cells, especially CD4+ T cells, in the pathogenesis of RA is substantial and includes 1) the correlation between prolonged CD4+ T-cell depletion and improvement in joint disease in the absence of observable changes in the levels of autoantibodies (rheumatoid factors) in the blood and joints, 2) the infiltration of the inflamed synovial tissues with T cells and, 3) the increased susceptibility of individuals to RA with certain HLA-DR haplotypes. The most direct evidence for the involvement of CD4+ T cells is provided by recent studies which demonstrate rapid improvement in the joint disease manifestations of RA following the infusion of anti-CD4 monoclonal **antibodies** (Herzog et al. 1989, Walker et al. 1989). It is unlikely that T cells alone are responsible for the joint injury in RA. Autoantibodies (rheumatoid factors) in the joint which contribute to the release of complement breakdown products, and to the secretion of cytokines such as IL-1 by macrophages must also play an important role. Indeed, depletion of CD4+ cells after TLI or **therapy** with monoclonal **antibody** reduces, but does not eliminate, joint disease activity. The residual joint disease activity is probably influenced by the continued contribution of autoantibodies to joint injury. Production of these autoantibodies may not be dependent on help from CD4+ cells, since little change is observed in autoantibody levels after CD4+ cell depletion. The mechanisms by which T cells mediate to the joint disease in RA are not clear. Little or no direct evidence of cytotoxic effects of T cells on autologous joint cells has been reported. Considerable evidence suggests that at least some T-cell cytokines (i.e., **TNF** alpha, IL-6) can contribute to the proliferation of synovial lining cells which results in the marked build-up of inflammatory tissue (pannus) in the joints of **patients** with RA (Firestein et al. 1990). In addition, T cells may recruit other joint cells, such as macrophages, to secrete cytokines (i.e., IL-1) which both contribute to synovial cell proliferation, and cartilage and bone degeneration. The marked reduction in the spontaneous secretion of IL-1 by synovial biopsies, and improvement in disease activity after TLI support this notion. Interestingly, the CD4+ T-cell lymphokines, IL-2 and IFN-gamma, were not spontaneously secreted in detectable quantities by synovial biopsies. This suggests that the pattern of lymphokines secreted by T cells in the joint in RA are not typical of that in delayed-type hypersensitivity reactions.(ABSTRACT TRUNCATED AT 400 WORDS)

6/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

07639187 91158187
Increased **TNF**-alpha secretion by alveolar macrophages from **patients** with **rheumatoid** **arthritis**.
Gosset P; Perez T; Lassalle P; Duquesnoy B; Farre JM; Tonnel AB; Capron A
Centre d'Immunologie et de Biologie Parasitaire, Unite mixte INSERM, CNRS, Lille, France.
Am Rev Respir Dis (UNITED STATES) Mar 1991, 143 (3) p593-7, ISSN 0003-0805 Journal Code: 426
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factor** alpha (**TNF**) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 **rheumatoid** **arthritis** (RA) **patients** without interstitial lung disease (ILD, Group 1) and 14 RA **patients** with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA **patients**. Spontaneous **TNF** production was significantly increased in Group 2 (2.5 +/- 0.5 ng/ml) as well as in Group 1 (2.4 +/- 0.4 ng/ml) compared with control subjects (0.43 +/- 0.1 ng/ml, p less than 0.001). In addition, AM from **patients** untreated or **treated** exclusively by nonsteroidal antiinflammatory drugs produced similar levels of **TNF**, whereas those receiving corticosteroids, second-line drugs (such as sulfasalazine, aurothiomalate, and methotrexate), or the combination of both **therapy** regimens released significantly less **TNF**. Interestingly, **TNF** was not different in both groups, but Group 2 had a markedly increased ratio of local immune

complex to albumin in bronchoalveolar lavage fluid (0.47 +/- 0.12 versus 0.07 +/- 0.02 in Group 1; p less than 0.002). **TNF** thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.

6/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

07623791 91142791
Methotrexate: mechanism of action in **rheumatoid** **arthritis**.
Segal R; Yaron M; Tartakovsky B
Department of Rheumatology, Ichilov Hospital, Tel-Aviv University, Sackler School of Medicine, Israel.
Semin Arthritis Rheum (UNITED STATES) Dec 1990, 20 (3) p190-200, ISSN 0049-0172 Journal Code: UMV
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Most studies of immune function in **rheumatoid** **arthritis** (RA) **patients** **treated** with methotrexate (MTX) show only marginal effects on humoral or cellular immune responses. These include measurements of lymphocyte subsets, proliferative responses to mitogens, immunoglobulin production, rheumatoid factor and immune complexes. The mechanism of action of MTX in RA might be more antiinflammatory than immunosuppressive. This is supported by the rapid clinical response to drug **treatment** and by data from in vitro and animal studies. The inhibition of interleukin-1 (IL-1) activity or other inflammatory cytokines by MTX may play an important role in the antiinflammatory effect of MTX. MTX effects in RA are not fully understood and further studies are needed to clarify its mechanism of action. MTX has crucial effects on the cascade of events initiated by some cytokines (IL-1, IL-6, **tumor** **necrosis** **factor**), which plays a major role in RA and other inflammatory diseases.

6/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

07540512 91059512
Cytokines and anticytokines.
Panayi GS
United Medical School, Guy's Hospital, London, UK.
Clin Exp Rheumatol (ITALY) Jul-Aug 1990, 8 Suppl 5 p65-6, ISSN 0392-856X Journal Code: DFA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The inflammation in the rheumatoid synovial membrane may be characterised by the concomitant presence of proinflammatory and anti-inflammatory mechanisms and mediators. These events may be spacially distributed within the tissue and may be visualised as waves of inflammation followed by waves of repair. The aim of **therapy** must be to enhance the anti-cytokine and reoperative processes over the inflammatory ones.

6/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

07536097 91055097
Cytokine regulation of colony-stimulating factor production in cultured human synovial fibroblasts: I. Induction of GM-CSF and G-CSF production by interleukin-1 and **tumor** **necrosis** **factor**.
Leizer T; Cebon J; Layton JE; Hamilton JA
Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia.
Blood (UNITED STATES) Nov 15 1990, 76 (10) p1989-96, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The cytokines, interleukin-1 (IL-1) and **tumor** **necrosis** **factor** (**TNF**), induce a dose-dependent production of both granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte CSF (G-CSF) in cultured human synovial cells, as measured by immunoassay. With IL-1, significant levels of both CSFs were first detected within 6 to 12 hours, with a maximum reached 24 to 48 hours after commencement of stimulation. A synergistic effect was detected between IL-1 and **TNF** in production of both CSFs in these cells. No evidence was obtained for the IL-1-induced effect to be mediated by induction of endogenous **TNF** nor for the **TNF** -induced stimulation to involve IL-1. IL-1-stimulated synovial cells were shown to secrete biologically active GM-CSF and G-CSF, which were specifically inhibited by their respective monoclonal **antibodies** . The transcription inhibitor, actinomycin D, and protein synthesis inhibitor, cycloheximide, inhibited the increase in GM-CSF and G-CSF production induced by IL-1 and **TNF**. Finally, other cytokines, IL-3, interferon gamma (IFN gamma), IL-2, platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and transforming growth factor alpha (TGF alpha), failed to stimulate either GM-CSF or G-CSF production, whether alone or in the presence of IL-1. These results suggest that cytokine-stimulated synovial fibroblasts may be a major source of intraarticular CSF production in the joints of **patients** with inflammatory **arthritis** ; as a result, monocyte/macrophages and granulocytes may be activated, leading to perpetuation of the inflammation and destructive events occurring in these lesions.

6/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

07509563 91028563
The inhibition of NK cell function by azathioprine during the **treatment** of **patients** with **rheumatoid** **arthritis**.
Cseuz R; Panayi GS
Division of Medicine, United Medical School, Guy's Hospital, London.
Br J Rheumatol (ENGLAND) Oct 1990, 29 (5) p358-62, ISSN 0263-7103 Journal Code: B1T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Treatment with azathioprine of **patients** with **rheumatoid** **arthritis** leads to a dramatic reduction in the 4 h NK cytotoxicity against K562 cells. The 24 h cytotoxicity against K562 and U937 cells, however, remains intact. The generation of cell-free supernatant cytotoxic factor(s) after incubating non-adherent mononuclear cells with U937 cells for 24 h is similar in the azathioprine **patients** and the controls. A large part of this supernatant cytotoxicity is due to **tumour** **necrosis** **factor** alpha which can be inhibited by a specific monoclonal **antibody** . The mechanism of the reduced 4 h NK cytotoxicity remains unknown but is probably not related to the anti-inflammatory properties of azathioprine.

6/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

07490157 91009157
Discoordinate expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases-1 in rheumatoid human synovial fibroblasts. Synergistic effects of interleukin-1 and **tumor** **necrosis** **factor** -alpha on stromelysin expression.
MacNaul KL; Chartrain N; Lark M; Tocci MJ; Hutchinson NI
Department of Molecular Immunology, Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065.
J Biol Chem (UNITED STATES) Oct 5 1990, 265 (28) p17238-45, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Primary and passaged human synovial fibroblasts isolated from rheumatoid pannus were **treated** with recombinant interleukin-1 (IL-1) alpha or beta, **tumor** **necrosis** **factor**-alpha (**TNF**), or phorbol myristate acetate (PMA) to determine the effects of these stimuli on the

relative expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases (TIMP). The steady-state mRNA levels for these genes and glyceraldehyde-3-phosphate dehydrogenase were determined on Northern blots. Immunoblot analyses of the conditioned media using monoclonal **antibodies** generated against recombinant human stromelysin, collagenase, or TIMP showed that protein levels reflected the corresponding steady-state mRNA levels. The results revealed that 1) stromelysin and collagenase were not always coordinately expressed; 2) IL-1 was more potent than **TNF** or PMA in the induction of stromelysin expression; 3) neither IL-1 nor **TNF** significantly affected TIMP expression; 4) PMA induced both metalloproteinase and TIMP expression; and 5) the combination of IL-1 plus **TNF** had a synergistic effect on stromelysin expression. Dose response and time course experiments demonstrated that the synergistic effect of IL-1 plus **TNF** occurred at saturating concentrations of each cytokine and lasted for 7 days. In summary, the ability of IL-1 and **TNF** to preferentially induce stromelysin and collagenase expression, versus TIMP, may define a pivotal role for these cytokines in the pathogenesis of **rheumatoid** **arthritis**.

6/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

07445868 90352868
Detection of transforming growth factor-beta in **rheumatoid** **arthritis** synovial tissue: lack of effect on spontaneous cytokine production in joint cell cultures.
Brennan FM; Chantry D; Turner M; Foxwell B; Maini R; Feldmann M
Charing Cross-Sunley Research Centre, London, England.
Clin Exp Immunol (ENGLAND) Aug 1990, 81 (2) p278-85, ISSN 0009-9104 Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The presence of transforming growth factor-beta (TGF-beta) in inflammatory joint disease was investigated. Synovial fluid from **patients** with **rheumatoid** **arthritis** (RA) and **patients** with other non-autoimmune inflammatory joint diseases contained high levels of both active and latent TGF-beta. Levels of active TGF-beta did not correlate with drug regimen in either **patient** group or with the recovery period in the individuals with non-RA joint disease. Freshly isolated synovial cells from individuals with RA were shown by Northern blotting to express the mRNA for TGF-beta 1 and to secrete latent TGF-beta protein which could be neutralized by **antibodies** to TGF-beta 1 and TGF-beta 2. Lipopolysaccharide-stimulated peripheral blood mononuclear cells from normal donors produced interleukin-1 (IL-1) and **tumour** **necrosis** **factor**-alpha (**TNF** -alpha) which was inhibited by pretreatment of these cells with recombinant TGF-beta. Cytokine production was not inhibited if the addition of TGF-beta was used after the inducing stimulus, suggesting that in activated cells cytokine production cannot be inhibited. This was confirmed by the observation that neither TGF-beta 1 or TGF-beta 2 inhibited spontaneous IL-1 or **TNF** -alpha production by rheumatoid synovial mononuclear cells in culture. These findings show that despite the presence of active TGF-beta in RA synovial joints and the spontaneous production of latent (potentially active) TGF-beta by RA cells in culture, additional TGF-beta did not inhibit ongoing cytokine synthesis in vitro. This suggests that TGF-beta may not inhibit cytokine production in the rheumatoid joint although it cannot be ruled out that in vivo TGF-beta already has an immunosuppressive effect which cannot be further increased in vitro by exogenous protein.

6/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

07443591 90350591
Inhibition of interleukin-1 release by IX 207-887.
Schnyder J; Bollinger P; Payne T
Sandoz Research Institute Berne Ltd., Switzerland.
Agents Actions (SWITZERLAND) Jun 1990, 30 (3-4) p350-62, ISSN 0065-4299 Journal Code: 2XZ

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Compound IX 207-887 is a novel antiarthritic agent which inhibits the release of interleukin-1 (IL-1) from human monocytes and mouse peritoneal macrophages in vitro at concentrations which are achieved **therapeutically** in human **rheumatoid** **arthritis** and in animal models of **arthritis**. In the present studies IL-1 activity in conditioned media, homogenates or lysates was monitored using four independent assay systems. Biologically active IL-1 was determined by, a) the induction of latent metalloproteinase-release from rabbit articular chondrocytes, which is relatively specific for IL-1 and b) by a sensitive thymocyte proliferation assay. Immunoreactive IL-1-beta was assayed by RIA and ELISA. In all test systems IX 207-887 significantly reduced both biologically active and immunoreactive IL-1 in culture media, whereas the levels of IL-1 in homogenates or lysates were either unaffected or only marginally reduced. The release of other monokines tested, such as interleukin-6 and **tumour** **necrosis** **factor** -alpha, and the secretion of lysozyme were only marginally influenced. IX 207-887 neither affected the adherence of human monocytes nor markedly inhibited IL-1 or IL-2-induced thymocyte proliferation. In the chondrocyte test no IL-1 **antagonistic** activity of IX 207-887 could be observed. All of these data indicate that IX 207-887 has the novel property of being an inhibitor of IL-1 release.

6/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

07421778 90328778
Cytokine production in the rheumatoid joint: implications for **treatment**.
Feldmann M; Brennan FM; Chantry D; Haworth C; Turner M; Abney E; Buchan G ; Barrett K; Barkley D; Chu A; et al
Charing Cross Sunley Research Centre, 1 Lurgan Avenue, Hammersmith, London.
Ann Rheum Dis (ENGLAND) Jun 1990, 49 (1) p480-6, ISSN 0003-4967
Journal Code: 62W
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Cytokines are protein mediators that play a part in inflammation, the immune response, cell growth, repair, and fibrosis. All of these are continuing processes in active **rheumatoid** **arthritis** (RA), and so it would be expected that many cytokines would be actively produced in RA joints. Here, the molecular strategies devised to study the possible role of cytokines in the pathogenesis of RA, are reviewed and some of the initial results described. The relative abundance of various cytokines is 'catalogued' and then attention is turned to an attempt to discover which cytokines are of major importance in the pathogenesis. Neutralising **antibodies** to cytokines were used for that purpose, and it was found that **tumour** **necrosis** **factor** alpha (**TNF** alpha) is one of the major signals regulating the production of interleukin-1 in the RA, but not in the osteoarthritic joint. To understand further the dynamics of the cytokine network localisation of the cytokine producing cells by immunostaining--for example, **TNF** alpha, is currently being established.

6/3,AB/24
DIALOG(R)File 155:MEDLINE(R)

07346810 90253810
Cytokines and growth regulation of synoviocytes from **patients** with **rheumatoid** **arthritis** and rats with streptococcal cell wall **arthritis**.
Remmers EF; Lafyatis R; Kumkumian GK; Case JP; Roberts AB; Sporn MB; Wilder RL
Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland 20892.
Growth Factors (SWITZERLAND) 1990, 2 (2-3) p179-88, ISSN 0897-7194
Journal Code: AOI

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Paracrine growth factors probably stimulate the pathologic proliferation of synovial fibroblast-like cells (synoviocytes) in **rheumatoid** **arthritis** (RA), but the relative importance of various factors is highly controversial. To address this problem, we compared the effects of highly purified or recombinant cytokines, in serum-free medium, on the in vitro long-term growth of synoviocytes from **patients** with RA and rats with streptococcal cell wall (SCW) **arthritis**. Of the factors tested (PDGF, aFGF, bFGF, EGF, TGF-beta, IL-1-alpha, **TNF**-alpha and IFN-gamma), PDGF, was clearly the most potent stimulant of long-term growth of both rat and human synoviocytes. The strong mitogenic activity of rheumatoid synovial fluids was significantly inhibited by neutralizing anti-PDGF **antibody**, thus confirming the importance of PDGF. EGF, TGF-beta, IL-1-alpha, **TNF** -alpha, and IFN-gamma had minimal effects. Similar to the effects on anchorage-independent growth, TGF-beta 1 and 2, inhibited serum- or PDGF-stimulated anchorage-dependent growth. Considered in the context of other reports, these data support the view that cytokines such as PDGF, and possibly aFGF and bFGF, play major roles in stimulating synoviocyte hyperplasia in RA and SCW **arthritis**, whereas TGF-beta may inhibit synoviocyte growth.

6/3,AB/25
DIALOG(R)File 155:MEDLINE(R)

07329607 90236607
Cachectin/**tumour** **necrosis** **factor**-alpha in the circulation of **patients** with rheumatic disease.
Maury CP; Teppo AM
Fourth Department of Medicine, University of Helsinki, Finland.
Int J Tissue React (SWITZERLAND) 1989, 11 (4) p189-93, ISSN 0250-0868
Journal Code: GTG
Languages: ENGLISH
Document type: JOURNAL ARTICLE
By means of a sensitive double-**antibody** radioimmunoassay, cachectin/**tumour** **necrosis** **factor**-alpha (**TNF**) was measured in sera from 51 **patients** with rheumatic disease. Elevated levels of circulating cachectin/**TNF** were observed in 46% of **patients** with **rheumatoid** **arthritis** (RA; p less than 0.001 versus blood donors) and in 29% of **patients** with systemic lupus erythematosus (SLE; p less than 0.05 versus blood donors). Marked elevation of cachectin/**TNF** occurred in both RA and SLE **patients** in connection with severe infections. The results show that cachectin/**TNF** is present in the circulation of certain **patients** with rheumatic disease, and that although the median cachectin **TNF** level in SLE **patients** is lower than that in RA **patients**, the cachectin/**TNF** response in SLE **patients** to severe infections is similar to that in RA **patients**.

6/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

07294639 90201639
Ex vivo lipopolysaccharide-induced interleukin-1 secretion from murine peritoneal macrophages inhibited by probucol, a hypocholesterolemic agent with antioxidant properties.
Ku G; Doherty NS; Schmidt LF; Jackson RL; Dinerstein RJ
Merrell Dow Research Institute, Cincinnati, Ohio 45215.
FASEB J (UNITED STATES) Apr 1 1990, 4 (6) p1645-53, ISSN 0892-6638
Journal Code: FAS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Probucol, 4,4'-(isopropylidenedithio)bis(2,6-di-tert-butyl-phenol), has been shown to inhibit atherogenesis in genetically hypercholesterolemic (Watanabe) rabbits. Since atherosclerotic lesions contain macrophages capable of screting interleukin 1 (IL 1) and other cytokines that could contribute to the pathogenesis of the disease, we have investigated whether probucol affects IL 1 secretion. Resident peritoneal macrophages from mice dosed with probucol secreted 40-80% less IL 1 than macrophages from control

Languages: ENGLISH
Document type: JOURNAL ARTICLE
The cytotoxic cytokines, **tumor** **necrosis** **factor** -alpha or cachectin and lymphotoxin (LT), are mediators of bone resorption and of inflammation and may have relevance in **rheumatoid** **arthritis**. Using mononuclear cells (MC) isolated from matched peripheral blood (PB) and synovial fluid (SF) of 13 **patients** with **rheumatoid** **arthritis**, we examined the generation of cytotoxic activity in a bioassay capable of detecting both **TNF** and LT. Synovial fluid mononuclear cells (MC) released significantly more cytotoxic activity than did matched PBMC, both spontaneously and following activation with phytohemagglutinin P (PHA). When PB and SFMC were stimulated with the combination of PHA plus phorbol-12-myristate acetate (PMA), the resulting culture supernatants possessed comparable cytotoxic activity. Neutralization studies employing anti-cytokine **antibodies** indicated that **TNF** represented 43 and 59% of the cytotoxic activity in the PHA plus PMA-induced culture supernatants from PB and SF, respectively. Since no inhibition was noted with **antibodies** to LT, the nature of the remaining approximately 50% of the cytotoxic activity was not determined. In PB and SF culture supernatants, obtained both spontaneously and following PHA activation, the concentration of **TNF** measured by ELISA significantly correlated with the level of cytotoxicity. As with the cytotoxic activity, the concentration of **TNF** was greater in the PHA-stimulated supernatants from SF than from PB. These observations suggest that **TNF** in the SF may contribute to the inflammation and bone destruction observed in **rheumatoid** **arthritis**.

6/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

07181616 90088616
Interleukin-1-inhibitory IgG in sera from some **patients** with **rheumatoid** **arthritis**.
Suzuki H; Akama T; Okane M; Kono I; Matsui Y; Yamane K; Kashiwagi H
Department of Rheumatology, University of Tsukuba, Ibaraki-ken, Japan.
Arthritis Rheum (UNITED STATES) Dec 1989, 32 (12) p1528-38, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Inhibition of interleukin-1 alpha (IL-1 alpha) activity was detected in 7 of 41 serum samples from **patients** with **rheumatoid** **arthritis** (RA). These 7 sera inhibited not only IL-1 alpha-induced endothelial cell adherence to neutrophils, but also IL-1 beta-induced endothelial cell adherence, although to a lesser extent. These sera showed no influence on **tumor** **necrosis** **factor** -induced endothelial cell adherence. No inhibitory activity was found in 40 sera from normal control subjects. Studies to further examine these effects included gel filtration analysis of 2 of the RA sera. The inhibitory activity was eluted near Mr 158 kd and above Mr 250 kd. Analysis by protein A affinity chromatography showed that IL-1-inhibitory activity was present in protein A-binding fractions. Purified IgG (by DE-52 column chromatography) from RA **patients** was found to be as potent an inhibitor as the protein A-binding fractions, which suggests that the major inhibitory activity in RA sera is attributable to IgG molecules. These purified IgG molecules also inhibited IL-1-induced proliferation of mouse thymocytes but did not influence IL-2-dependent proliferation of the CTLL-2 murine T cell line. The 7 **patients** whose sera showed IL-1-inhibitory activity had mild RA and low titers of rheumatoid factor. The findings, taken together, suggest a possible regulatory role of IL-1-inhibitory IgG in RA disease activity.

6/3,AB/30
DIALOG(R)File 155:MEDLINE(R)

07027982 89329982
Inhibitory effect of **TNF** alpha **antibodies** on synovial cell interleukin-1 production in **rheumatoid** **arthritis**.
Brennan FM; Chantry D; Jackson A; Maini R; Feldmann M
Charing Cross Sunley Research Centre, Hammersmith, London.
Lancet (ENGLAND) Jul 29 1989, 2 (8657) p244-7, ISSN 0140-6736

Journal Code: LOS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effect of **tumour** **necrosis** **factor** (**TNF** alpha) **antibodies** on synovial cell interleukin-1 (IL-1) production was investigated in 7 **patients** with **rheumatoid** **arthritis** and in 7 with osteoarthritis. Synovial cell IL-1 production was significantly reduced by anti-**TNF** alpha **antibody** in cultures from **patients** with **rheumatoid** **arthritis**, but antilymphotoxin **antibody** did not have this effect (except in 1 culture). In cultures from **patients** with osteoarthritis spontaneous IL-1 production was low, despite high concentrations of **TNF** alpha, and IL-1 production was not inhibited by anti-**TNF** alpha **antibody**. In **rheumatoid** **arthritis**, **TNF** alpha may be the main inducer of IL-1, and anti-**TNF** alpha agents may be useful in **treatment**.

6/3,AB/31
DIALOG(R)File 155:MEDLINE(R)

07000375 89302375
Synovial localization of **tumor** **necrosis** **factor** in **patients** with **rheumatoid** **arthritis**.
Husby G; Williams RC Jr
Department of Medicine, University of New Mexico School of Medicine, Albuquerque 87131.
J Autoimmun (ENGLAND) Aug 1988, 1 (4) p363-71, ISSN 0896-8411
Journal Code: ADL
Contract/Grant No.: AMAI13690; 13814
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tissue localization of **tumor** **necrosis** **factor** (**TNF** alpha) was examined in synovial tissues from 10 **patients** with active **rheumatoid** **arthritis** (RA) and three osteoarthritis controls using both monoclonal and polyclonal **antibodies** to **TNF** alpha and immunoperoxidase technique. No prominent staining for **TNF** alpha was noted in any of the osteoarthritis non-inflammatory synovial samples; however, six out of 10 RA synovial tissues displayed strongly positive tissue distribution of **TNF** alpha epitopes particularly within synovial lining cells, and interstitial monocyte/macrophage cells within inflammatory infiltrates. The amounts of **TNF** alpha visualized within synovial lining cells appeared to parallel the extent of inflammatory cell collections within the rheumatoid synovial tissues examined. Similar studies using renal biopsy tissues from seven **patients** with Systemic Lupus Erythematosus (SLE) nephritis (including diffuse proliferative nephritis, nephrotic syndrome, focal glomerulonephritis, and membranous nephritis) showed no tissue localization of **TNF** alpha. These findings emphasize that a potent lymphokine (**TNF** alpha), which may be important in the underlying inflammatory process, appears to be localized and perhaps produced by synovial lining cells within active RA synovial tissues.

6/3,AB/32
DIALOG(R)File 155:MEDLINE(R)

06871015 89173015
Characteristics of human synovial fibroblast activation by IL-1 beta and **TNF** alpha.
Gitter BD; Labus JM; Lees SL; Scheetz ME
Lilly Research Laboratories, Eli Lilly & Co., Lilly Corporate Center, Indianapolis, Indiana 46285.
Immunology (ENGLAND) Feb 1989, 66 (2) p196-200, ISSN 0019-2805
Journal Code: GH7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human synovial fibroblast cell lines (HSN), established from tissues obtained from the knee joints of **arthritis** **patients** undergoing arthoplasty, were used to investigate the effects of human interleukin-1 (IL-1) beta and **tumour** **necrosis** **factor** (**TNF**)alpha on proliferation and prostaglandin E2 (PGE2) secretion. IL-1 beta and **TNF**

alpha were equipotent stimulators of HSN proliferation. Classical non-steroidal anti-inflammatory drugs and glucocorticoids significantly augmented this effect. In addition, IL-1 beta and **TNF** alpha were potent inducers of PGE2 production while exogenous PGE2 was growth inhibiting. These data suggest that the secretion of PGE2 by monokine-stimulated HSN exerts a negative feedback signal. Further examination of IL-1 beta- and **TNF** alpha-induced PGE2 secretion revealed IL-1 beta to be a more potent stimulator; however, this observation may be due, in part, to differences in the kinetics of induction. Rabbit anti-IL-1 beta and anti-**TNF** alpha specifically neutralized both proliferation and PGE2 production induced by these monokines, but anti-IL-1 beta (or anti-IL-1 alpha) did not block **TNF** alpha activity. It is unclear whether **TNF** alpha stimulates HSN to produce IL-1, but the **antibody** data suggest that extracellular IL-1 is not responsible for **TNF** alpha in vitro activity.

6/3,AB/33
DIALOG(R)File 155:MEDLINE(R)

06788215 89090215
Interleukin-1 and **tumour** **necrosis** **factor** mRNA expression in **rheumatoid** **arthritis**: prolonged production of IL-1 alpha.
Buchan G; Barrett K; Turner M; Chantry D; Maini RN; Feldmann M
Charing Cross Sunley Research Centre, Hammersmith, London, UK.
Clin Exp Immunol (ENGLAND) Sep 1988, 73 (3) p449-55, ISSN 0009-9104
Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In **rheumatoid** **arthritis** there is a chronic immune and inflammatory reaction which can lead to the destruction of the diseased joint. Cytokine gene expression was studied in synovial cells using cDNA probes specific for human interleukin 1 (IL-1), -alpha and IL-1 beta, **tumour** **necrosis** **factor** (**TNF**), -alpha and **TNF** beta (lymphotoxin); protein molecules which induce cartilage degradation and bone resorption. In all cases studied, IL-1 mRNA was present in freshly isolated synovial cells from fluid or membrane. Compared to levels of IL-1 mRNA found in optimally activated normal blood mononuclear cells, the levels of IL-1 alpha mRNA were high in seven of the nine **patients** studied, whereas IL-1 beta mRNA, the dominant form in blood, was relatively lower. **TNF** alpha and **TNF** beta mRNA were also detected. Rheumatoid synovial cells, cultured without any stimulus, continued to express high levels of IL-1 alpha mRNA for up to 5 days, compared to the 24 h response of activated blood cells; IL-1 beta mRNA in culture was also prolonged. Cultures of rheumatoid joint cells produced IL-1 bioactivity, with roughly equal amounts of IL-1 alpha and beta, as assessed using neutralizing **antibodies**. **TNF** bioactivity was also detected which may be of importance as **TNF** induces the production of IL-1. The finding of these mediators produced in large amounts in active rheumatoid synovial cells suggests that mutually stimulatory cell interactions, mediated by these molecules, may be important in the chronic inflammation and tissue destruction in **rheumatoid** **arthritis**.

6/3,AB/34
DIALOG(R)File 155:MEDLINE(R)

06722834 89024834
Tumour **necrosis** **factor** in synovial exudates.
Di Giovine FS; Nuki G; Duff GW
University of Edinburgh Department of Medicine, UK.
Ann Rheum Dis (ENGLAND) Sep 1988, 47 (9) p768-72, ISSN 0003-4967
Journal Code: 62W
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The actions of **tumour** **necrosis** **factor** (**TNF**) include resorption of bone and cartilage, suggesting a potential role in the pathogenesis of **arthritis**. **TNF** activity was looked for in synovial fluids from 137 **patients** with different rheumatic diseases. Unfractionated samples were tested in the L929 bioassay. Significant **TNF** activity that was neutralised by monoclonal **antibody** to **TNF**

alpha occurred in 13 (30%) of 44 samples. Raised **TNF** levels were not associated with any particular disease type or routine laboratory markers of inflammation but were related to disease duration in osteoarthritis. The finding of biologically active **TNF** in symptomatic joints of arthritic **patients** supports the idea that it may contribute to the pathogenesis of joint damage in chronic rheumatic diseases.

6/3,AB/35
DIALOG(R)File 155:MEDLINE(R)

06701762 89003762
Cytokines in synovial fluid: II. The presence of **tumour** **necrosis** **factor** and interferon.
Hopkins SJ; Meager A
University of Manchester Rheumatic Diseases Centre, Hope Hospital, Salford, UK.
Clin Exp Immunol (ENGLAND) Jul 1988, 73 (1) p88-92, ISSN 0009-9104
Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cytokine-specific monoclonal **antibodies** were used in enzyme-linked immunoadsorbant assays (ELISA) to examine a variety of synovial fluids for the presence of cytokines which might be expected to play some part in the pathology of **arthritis**. Low, but significant, levels of **tumour** **necrosis** **factor** alpha (**TNF**-alpha) were present in the majority of synovial fluids obtained from **rheumatoid** **arthritis** **patients** with a sero-positive history. Low levels of interferon (IFN)-alpha and IFN-gamma were also detected, but only IFN-alpha was significantly increased in the sero-positive group. **Tumour** **necrosis** **factor** beta (**TNF** -beta) was present only in trace amounts. These results suggest that the presence of cytokines, such as **TNF**-alpha and IFN-alpha in synovial fluid may be associated with tissue changes observed in rheumatoid joint disease and thus contribute to the pathology of the **arthritis**, but support evidence for the minimal role likely to be played by IFN-gamma in the joint pathology of **rheumatoid** **arthritis**.

6/3,AB/36
DIALOG(R)File 155:MEDLINE(R)

06408311 88053311
Radioimmunoassay of **tumor** **necrosis** **factor** in serum.
Teppo AM; Maury CP
IV Department of Medicine, University Central Hospital, Helsinki, Finland.
Clin Chem (UNITED STATES) Nov 1987, 33 (11) p2024-7, ISSN 0009-9147
Journal Code: DBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We present a double-**antibody** radioimmunoassay for determination of the concentration of **tumor** **necrosis** **factor** (**TNF**) in serum. **TNF** in serum competes with a fixed amount of 125I-labeled **TNF** for the binding sites of specific rabbit **antibodies**. The bound **TNF** is precipitated with Sepharose-bound anti-rabbit IgG, then centrifuged, and the radioactivity of the pellets is counted. The detection limit of the assay is 7 ng/L (B0-3 SD). Bound radioactivity in the range of 10% to 90% of the B0 counts corresponds to **TNF** concentrations of 26 to 10,000 ng/L. Of 40 sera from healthy subjects, 21 (53%) contained **TNF** concentrations greater than 7 ng/L (range 8-40 ng/L). Some **patients** with parasitic or neoplastic disease and **patients** with septic shock had highly increased **TNF** values. Three of the 14 sera (21%) from **patients** with **rheumatoid** **arthritis** had **TNF** concentrations greater than 40 ng/L.
?DOGOFF

S1 31 ((TNF?/TI OR (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?/TI) AND ARTHRITIS) AND PY=1990:1991

?Ds1/3,ab/all

1/3,AB/1

DIALOG(R)File 155:MEDLINE(R)

08154121 92292121

Interleukin 1 and **tumor** **necrosis** **factor**-alpha synergistically increase the production of interleukin 6 in human synovial fibroblast.

Harigai M; Hara M; Kitani A; Norioka K; Hirose T; Hirose W; Suzuki K; Kawakami M; Masuda K; Shinmei M; et al

First Department of Medicine, National Defense Medical College, Saitama, Japan.

J Clin Lab Immunol (SCOTLAND) Mar **1991**, 34 (3) p107-13, ISSN 0141-2760 Journal Code: J3K

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have previously reported that synovial cells could participate in B cell differentiation processes in rheumatoid **arthritis** (RA) by producing interleukin-6 (IL-6) spontaneously or in response to interleukin-1 (IL-1) stimulation. In this paper, we examined the effects of tumor necrosis factor-alpha (TNF-alpha) on IL-6 production by human synovial fibroblasts. TNF-alpha, as well as IL-1, is a putative relevant molecule in the inflammatory process and in articular destruction in RA. Both IL-1 and TNF-alpha induced IL-6 production by synovial fibroblasts in a dose dependent manner. When synovial fibroblasts were stimulated by IL-1 and TNF-alpha in combination, IL-6 production increased synergistically after 48 hr of a 72 hr culture period. Kinetic studies revealed that the presence of both cytokines at the early phase of stimulation was required for the synergistic effect. These results suggest that TNF-alpha could be involved in a cytokine network in the affected joints of RA and could contribute synergistically with IL-1 to the IL-6 production by synovial fibroblasts in vivo.

1/3,AB/2

DIALOG(R)File 155:MEDLINE(R)

08062796 92200796

Tumour **necrosis** **factor** alpha and interleukin-2 in plasma from rheumatoid **arthritis** patients in relation to disease activity [see comments]

Espersen GT; Vestergaard M; Ernst E; Grunnet N

Department of Clinical Immunology, Aalborg Hospital, Denmark.

Clin Rheumatol (BELGIUM) Dec **1991**, 10 (4) p374-6, ISSN 0770-3198 Journal Code: D16

Comment in Clin Rheumatol 1993 Jun;12(2):285-6

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Tumour necrosis factor alpha (TNF alpha) and interleukin-2 (IL-2) are potential immunological mediators of pathogenetic changes in rheumatoid **arthritis**. We measured the concentrations of TNF alpha and IL-2 in plasma from 2 groups of patients suffering from rheumatoid **arthritis** (RA). One group had high and one had low disease activity. In addition, in connection with steroid treatment in the high disease activity group, TNF alpha was significantly increased in plasma from RA patients with high disease activity compared with those of low disease activity ($p = 0.0009$). Furthermore, TNF alpha decreased significantly in relation to steroid medication, parallel to clinical improvement ($p = 0.016$). All IL-2 concentration measurements were within the estimated normal range. The increased TNF alpha plasma levels in patients with rheumatoid **arthritis** with high disease activity, might result from activated white mononuclear cells in the inflamed joints. This might, in part, support the theory that TNF alpha is a possible mediator of pathogenetic changes known to occur in rheumatoid **arthritis**.

1/3,AB/3

DIALOG(R)File 155:MEDLINE(R)

Division of Clinical Immunology, Mathilda and Terence Kennedy Institute of Rheumatology, Hammersmith, London, England.
Arthritis Rheum (UNITED STATES) Sep **1991**, 34 (9) p1125-32, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using immunoaffinity-purified polyclonal anti-human recombinant tumor necrosis factor alpha (TNF alpha) F(ab')2 fragments and immunohistochemical techniques, the cells that make TNF alpha were localized in the inflamed synovial tissue of patients with rheumatoid **arthritis** (RA) and osteoarthritis (OA). Anti-TNF alpha antibody-stained cells were demonstrated in 9 of 11 RA and 2 of 4 OA but none of 5 normal synovial membranes examined. In RA, 26-64% of the lining layer cells were positive for TNF alpha. In the interaggregate area, 10-30% of the cells contained TNF alpha, often in a perivascular distribution, and up to 19% of the cells in lymphoid aggregates stained for TNF alpha. Some endothelial cells also stained with these antibodies. In OA tissues, the TNF alpha-containing cells were found predominantly in the deeper layer. Cells containing TNF alpha were also found at the cartilage-pannus junction in all 4 RA specimens examined. Double immunofluorescence analysis demonstrated that most TNF alpha-secreting cells in the RA synovial membrane expressed the monocyte/macrophage marker antigens CD11b and CD14, and a few expressed the T cell marker CD3. Our findings provide histologic evidence that TNF alpha is locally produced in the lining and deeper layers of the synovium by cells of the monocyte/macrophage lineage, supporting its role in inflammation. Further, our findings demonstrate that TNF alpha is produced by cells at the cartilage-pannus junction, which could affect chondrocyte metabolism, leading to the cartilage degradation in RA.

1/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

07870169 92008169
Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid **arthritis**: regulation by **tumor** **necrosis** **factor** -alpha.
Haworth C; Brennan FM; Chantry D; Turner M; Maini RN; Feldmann M
Charing Cross Sunley Research Centre, Hammersmith, London, GB.
Eur J Immunol (GERMANY) Oct **1991**, 21 (10) p2575-9, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Granulocyte-macrophage colony-stimulating factor (GM-CSF), in addition to being a growth factor for granulocytes and macrophages, is an activator of cells of the monocyte/macrophage lineage and induces HLA class II expression and cytokine synthesis in these target cells. Macrophage activation and class II expression are prominent features in rheumatoid **arthritis** (RA) joints, but the mechanism of their stimulation is not understood, since interferon-gamma, the major stimulus of class II expression, is not usually detectable at the protein level in synovial cell culture supernatants. We have, therefore, studied GM-CSF expression in cultures of cells derived from joints affected by RA and osteoarthritis (OA), and show that GM-CSF is produced spontaneously both by RA synovial cells and to a lesser extent by OA synovial cells in the absence of extrinsic stimuli. GM-CSF production continues for the 5-day duration of the culture period. Using neutralizing antibodies to tumor necrosis factor (TNF)-alpha we demonstrated that GM-CSF production in RA synovial cell cultures is dependent on the continued presence of active TNF-alpha. This result supports our concept that continued activation of the cytokine network is a marked feature of RA, and that TNF-alpha plays a pivotal role in this network, by regulating the production of other pro-inflammatory cytokines, such as interleukin 1, as demonstrated previously, and GM-CSF.

1/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

07868267 92006267
Identification of the major fibroblast growth factors released

spontaneously in inflammatory **arthritis** as platelet derived growth factor and **tumour** **necrosis** **factor**-alpha.
Thornton SC; Por SB; Penny R; Richter M; Shelley L; Breit SN
Centre for Immunology, St Vincent's Hospital, Sydney, Australia.
Clin Exp Immunol (ENGLAND) Oct **1991**, 86 (1) p79-86, ISSN 0009-9104 Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Rheumatoid **arthritis** is characterized by chronic inflammation and proliferation of a number of important elements within the joint including the synovial fibroblasts. Elevated levels of a number of cytokines such as Il-1, IL-2, IL-6, interferon-gamma (IFN-gamma), transforming growth factor-beta and tumour necrosis factor-alpha (TNF-alpha) have been detected in the synovial fluid of patients with rheumatoid **arthritis** and other inflammatory arthritides. It seems likely that local release of such mediators may be responsible for the proliferation and overgrowth of connective tissue elements in these disorders. In order to ascertain whether there was evidence to suggest local production or release of fibroblast growth factors in the joint in inflammatory **arthritis**, and to determine their identity, cells were obtained from the synovial fluid of 15 patients with chronic inflammatory arthritides. All subjects' synovial fluid cells spontaneously released growth factor activity for fibroblasts. This was present in large amounts, being detectable in culture supernatants diluted to a titre of at least 1/625. By a series of depletion experiments using solid-phase bound antibodies to cytokines, it was possible to demonstrate that this activity was due to TNF-alpha and platelet-derived growth factor (PDGF). Thus, this study showed for the first time that functionally active PDGF was released from synovial fluid cells. Both PDGF and TNF-alpha appeared to contribute in approximately equal amounts to this fibroblast growth factor activity, and were synergistic in effect. Thus this study provides evidence for the local production and release of these two cytokines and suggests that together they are the dominant factors in fibroblast proliferation within the synovial cavity.

1/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

07836652 91355652
Elevated levels of circulating **tumor** **necrosis** **factor**-alpha, interferon-gamma, and interleukin-2 in systemic reactions induced by anti-CD4 therapy in patients with rheumatoid **arthritis** [letter]
Horneff G; Krause A; Emmrich F; Kalden JR; Burmester GR
Cytokine (UNITED STATES) May **1991**, 3 (3) p266-7, ISSN 1043-4666 Journal Code: A52
Languages: ENGLISH
Document type: LETTER

1/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

07781730 91300730
Effects of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, interferon-gamma (IFN-gamma), **tumour** **necrosis** **factor** -alpha (**TNF** -alpha) and IL-6 on the production of immunoreactive IL-1 and **TNF**-alpha by human monocytes.
Danis VA; Franic GM; Rathjen DA; Brooks PM
Kolling Institute, Royal North Shore Hospital, Sydney, Australia.
Clin Exp Immunol (ENGLAND) Jul **1991**, 85 (1) p143-50, ISSN 0009-9104 Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effects of GM-CSF, IL-2, IFN-gamma, TNF-alpha and IL-6 on the production of IL-1 (both secreted and cell associated) and TNF-alpha by peripheral blood monocytes were studied. Monocytes were cultured for 20 h in suspension and in serum-free conditions which minimized background stimulation of monokine production. GM-CSF, IL-2 and TNF-alpha directly induced the production of cell-associated IL-1 but little or no IL-1 or TNF-alpha secretion. Combination of GM-CSF with IFN-gamma, IL-2 or

TNF-alpha synergistically enhanced IL-1 secretion and had an additive effect on cell-associated IL-1 production. Combination of IL-2 with IFN-gamma or TNF-alpha also synergistically enhanced IL-1 secretion but the effect on cell-associated IL-1 production was less than additive. GM-CSF synergistically enhanced TNF-alpha secretion induced by IFN-gamma but not by lipopolysaccharide. GM-CSF did not enhance TNF-alpha secretion induced by IL-2 or TNF-alpha. In contrast, IL-2 synergistically enhanced TNF-alpha secretion induced by IFN-gamma. These results are discussed in relation to cytokine involvement in rheumatoid **arthritis**.

1/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

07726170 91245170
Induction of suppurative **arthritis** in rabbits by Haemophilus endotoxin, **tumor** **necrosis** **factor**-alpha, and interleukin-1 beta.
Saez-Llorens X; Jafari HS; Olsen KD; Nariuchi H; Hansen EJ; McCracken GH Jr
Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas 75235-9063.
J Infect Dis (UNITED STATES) Jun **1991**, 163 (6) p1267-72, ISSN 0022-1899 Journal Code: IH3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Because Haemophilus influenzae type b (Hib) is the principal cause of suppurative **arthritis** in young children and its lipooligosaccharide (LOS) is thought to be the main virulence factor, Hib endotoxin was evaluated for its ability to induce synovial inflammation in rabbits. Also, the role of the cytokines tumor necrosis factor-alpha (TNF alpha) and interleukin-1 beta (IL-1 beta) in mediating the synovial inflammatory process was studied. Intraarticular inoculation of 2 pg to 20 ng of Hib LOS produced a dose-dependent increase in concentrations of leukocytes and protein in synovial lavage fluid that was significantly modulated by concomitant administration of rabbit TNF alpha- and rabbit IL-1 beta-specific antibodies. Inoculation of joints with either 10(4) IU of rabbit TNF alpha or 10 ng recombinant rabbit IL-beta induced synovial inflammatory changes similar to those observed after LOS intraarticular challenge. These data provide evidence for the role of Hib LOS in inducing suppurative **arthritis** and for the critical participation of TNF alpha and IL-1 beta in the initial events of the synovial inflammatory response.

1/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

07706967 91225967
Chronic inflammatory joint diseases: natural inhibitors of interleukin 1 and **tumor** **necrosis** **factor** alpha.
Dayer JM
Division of Immunology and Allergy, University Hospital, Geneva, Switzerland.
J Rheumatol Suppl (CANADA) Feb **1991**, 27 p71-5, ISSN 0380-0903 Journal Code: JWY
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Cytokines play a major role in the initiation of the immune response or acute inflammatory events, and in the transition to or persistence of chronic inflammation, which eventually lead to tissue destruction and/or fibrosis. Cytokine inhibitors, peptides, have been recently isolated from normal or pathological biological fluids and cell culture supernatants. They can impede either acute inflammation or the transition to chronic inflammation. Two well defined molecules have been identified, interleukin 1 inhibitor, and tumor necrosis factor alpha inhibitor. They may be part of an attempt to control the expansion of the inflammation. The balance between cytokines and their inhibitors is of importance in the control of inflammatory diseases, and the lack of natural cytokine inhibitors may play a major part in maintaining inflammatory conditions.

1/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

07706472 91225472
Cytokines in chronic inflammatory **arthritis**. VI. Analysis of the synovial cells involved in granulocyte-macrophage colony-stimulating factor production and gene expression in rheumatoid **arthritis** and its regulation by IL-1 and **tumor** **necrosis** **factor**-alpha.
Alvaro-Gracia JM; Zvaifler NJ; Brown CB; Kaushansky K; Firestein GS
Division of Rheumatology, University of California, San Diego 92103.
J Immunol (UNITED STATES) May 15 **1991**, 146 (10) p3365-71, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AR-14916, AR, NIAMS; AR-39576, AR, NIAMS; AR-40525, AR, NIAMS; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Granulocyte-macrophage CSF (GM-CSF) is a potent stimulator of macrophages and neutrophils and is produced by rheumatoid **arthritis** (RA) synovium. We now report studies that identify some of the synovial cells and cytokines responsible for local GM-CSF production and gene expression in RA. GM-CSF was assayed by ELISA in supernatants from cultured RA fibroblast-like synoviocytes stimulated with various cytokines (IL-1 beta, TNF-alpha, macrophage-CSF, IFN-gamma, IL-6, and TGF-beta). Immunoreactive GM-CSF was detected in IL-1 beta and TNF-alpha-stimulated cultures, but not in cells cultured in medium or stimulated with any of the other cytokines. IL-1 and TNF-alpha had a synergistic effect on GM-CSF production. GM-CSF gene expression by fibroblast-like synoviocytes was analyzed by ribonuclease protection assay, Northern blot analysis, and in situ hybridization. Both IL-1 beta and TNF-alpha induced GM-CSF mRNA accumulation, with a maximum effect after 4 h of stimulation. We then studied GM-CSF production by macrophage-like synoviocytes (MLS) isolated from fresh synovial specimens by flow microfluorimetry. Fresh MLS spontaneously secreted the cytokine and exogenous IL-1 beta or TNF-alpha had no effect. After 1 wk in culture, additional stimulation with IL-1 beta or TNF-alpha was required for GM-CSF production. Finally, in situ hybridization performed on freshly isolated subpopulations of synovial cells, identified GM-CSF RNA transcripts in MLS.

1/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

07666621 91185621
Urate crystals stimulate production of **tumor** **necrosis** **factor** alpha from human blood monocytes and synovial cells. Cytokine mRNA and protein kinetics, and cellular distribution.
di Giovine FS; Malawista SE; Thornton E; Duff GW
University Department of Medicine, Northern General Hospital, Edinburgh, United Kingdom.
J Clin Invest (UNITED STATES) Apr **1991**, 87 (4) p1375-81, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: AR-10493, AR, NIAMS; AR-07107, AR, NIAMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Crystals of monosodium urate (MSU) provide a dose-dependent stimulus for the production by human blood monocytes of tumor necrosis factor (TNF), a cytokine with proinflammatory properties; TNF activity was inhibited selectively by monoclonal antibody to TNF alpha. Biologically active cell-associated TNF activity peaked at 3 h and was exceeded at 6 h by extracellular activity, which peaked at 12-18 h. Comparable kinetics were observed with immunoreactive TNF alpha. TNF alpha mRNA accumulation in monocytes stimulated with MSU crystals appeared as a single peak at 2-4 h, kinetics compatible with rapid production of a short half-life transcript. In contrast, crystals of calcium pyrophosphate or of hydroxyapatite did not stimulate significant production of TNF or of message. Fresh tophaceous material from a patient with gout contained significant levels of TNF alpha and cells cultured from the tophus produced TNF alpha in vitro. In rheumatoid synovial cells, spontaneous release of TNF alpha was increased by in vitro exposure to MSU crystals. Taken together with earlier work, these results support an expanded view of gouty inflammation in which the

crystal-stimulated production of cytokines provides a crucial link between crystal deposition and many of the clinical and pathological facts of both acute and chronic gouty **arthritis**.

1/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

07649444 91168444
Peripheral blood monocytes from patients with reactive **arthritis** show normal production of **tumour** **necrosis** **factor**-alpha [letter]
Repo H; Lauhio A; Jaattela M; Saikku P; Leirisalo-Repo M
Clin Exp Immunol (ENGLAND) Mar **1991**, 83 (3) p516-7, ISSN 0009-9104 Journal Code: DD7
Languages: ENGLISH
Document type: LETTER

1/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

07645709 91164709
Interleukin-2, soluble interleukin-2 receptor and **tumor** **necrosis** **factor** in sera from patients with rheumatoid **arthritis**.
Corvetta A; Luchetti MM; Pomponio G; Della Bitta R; Recchioni A; Strusi P ; De Sio G; Danieli G
Istituto di Clinica Medica Generale e Terapia Medica, Universita degli Studi di Ancona.
Ric Clin Lab (ITALY) Oct-Dec **1990**, 20 (4) p275-81, ISSN 0390-5748 Journal Code: TEA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Interleukin-2 (IL-2), soluble interleukin-2 receptor (IL-2R) and tumor necrosis factor (TNF) have been measured in sera from 47 patients affected by classic rheumatoid **arthritis** (RA) using an enzyme-linked immunosorbent assay. The patients were divided into 4 groups as follows: group A, 18 patients with inactive disease; group B, 19 patients with active disease under treatment with non-steroidal antiinflammatory drugs (NSAID) and second-line drugs; group C, 5 patients with active disease under treatment with NSAID and cyclosporine A (CSA) for at least 4 months; group D, 5 patients in the same condition as patients of group C, but treated with azathioprine (AZA) instead of CSA. IL-2 was undetectable in all patients except two, both characterized by active disease. Soluble IL-2R levels were above the upper limit of the normal range in most of the patients studied, but the mean value (+/- 1 SD) was significantly higher in patients of group B (1,288 +/- 421 U/ml) than in patients of group A (686 +/- 205 U/ml) and group C (842 +/- 414 U/ml). In two patients affected by active RA treated with pulse methylprednisolone therapy (1 g/day for 3 alternate days) the values of soluble IL-2R dropped from 948 to 662 U/ml and from 660 to 518 U/ml, respectively. No statistically significant correlation was observed between the serum level of IL-2R and the RF titre or percentage of C1q-binding activity, respectively. TNF was found within the normal range in all patients except one, who was characterized by active **arthritis**, high number of rheumatoid skin nodules and extremely high RF titre.(ABSTRACT TRUNCATED AT 250 WORDS)

1/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

07639187 91158187
Increased **TNF**-alpha secretion by alveolar macrophages from patients with rheumatoid **arthritis**.
Gosset P; Perez T; Lassalle P; Duquesnoy B; Farre JM; Tonnel AB; Capron A
Centre d'Immunologie et de Biologie Parasitaire, Unite mixte INSERM, CNRS, Lille, France.
Am Rev Respir Dis (UNITED STATES) Mar **1991**, 143 (3) p593-7, ISSN 0003-0805 Journal Code: 426
Languages: ENGLISH

Document type: JOURNAL ARTICLE
Tumor necrosis factor alpha (TNF) and interleukin-1 (IL-1) production by alveolar macrophages (AM) was evaluated in 17 rheumatoid **arthritis** (RA) patients without interstitial lung disease (ILD, Group 1) and 14 RA patients with clinical ILD (Group 2) in comparison with 10 control subjects. AM after recovery by bronchoalveolar lavage were selected by adherence, and then supernatants were collected after 3 or 24 h of culture. Results showed no modification of IL-1 synthesis in either group of RA patients. Spontaneous TNF production was significantly increased in Group 2 (2.5 +/- 0.5 ng/ml) as well as in Group 1 (2.4 +/- 0.4 ng/ml) compared with control subjects (0.43 +/- 0.1 ng/ml, p less than 0.001). In addition, AM from patients untreated or treated exclusively by nonsteroidal antiinflammatory drugs produced similar levels of TNF, whereas those receiving corticosteroids, second-line drugs (such as sulfasalazine, aurothiomalate, and methotrexate), or the combination of both therapy regimens released significantly less TNF. Interestingly, TNF was not different in both groups, but Group 2 had a markedly increased ratio of local immune complex to albumin in bronchoalveolar lavage fluid (0.47 +/- 0.12 versus 0.07 +/- 0.02 in Group 1; p less than 0.002). TNF thus appears an additional component of RA subclinical alveolitis in RA, but its prognostic value and its precise role in lung damage remain to be determined. Development of ILD requires certainly complex interactions of synergistic factors, possibly including local immune complexes detected in BAL fluids.

1/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

07608295 91127295
Estrogen inhibits release of **tumor** **necrosis** **factor** from peripheral blood mononuclear cells in postmenopausal women.
Ralston SH; Russell RG; Gowen M
Department of Human Metabolism and Clinical Biochemistry, University of Sheffield Medical School, England.
J Bone Miner Res (UNITED STATES) Sep **1990**, 5 (9) p983-8, ISSN 0884-0431 Journal Code: 130
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cytokines, such as interleukin-1 (IL-1) and tumor necrosis factors (TNF), produced by cells of the monocyte-macrophage lineage in the local bone microenvironment, are potentially important local regulators of bone turnover. To investigate whether the protective effects of estrogen against postmenopausal bone loss may be mediated by inhibition of cytokine release, we studied the effects of 17 beta-estradiol, dihydrotestosterone, and hydrocortisone on TNF release from human peripheral blood mononuclear cells (PBMC) in vitro. In unstimulated cells derived from eight postmenopausal women, seven of whom had osteoporotic vertebral fractures, 17 beta-estradiol inhibited TNF release in a dose-dependent manner between 10(-6) and 10(-12) M but had no consistent effect on cells derived from men or premenopausal women. Dihydrotestosterone in concentrations of up to 10(-6) M had no effect on TNF release in any patient group, whereas hydrocortisone at 10(-6) M was a potent inhibitor of TNF release in all groups. Since TNF is a potent stimulator of bone resorption, the inhibitory effect of estrogen on TNF release may be part of the mechanism by which it exerts a protective effect on the skeleton in postmenopausal women. These observations may also be relevant in other inflammatory diseases of connective tissue, such as rheumatoid **arthritis** , in which disease activity may fluctuate as estrogen levels change--during the menstrual cycle, in pregnancy, and after the menopause.

1/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

07560498 91079498
Analysis of IL-1 and **TNF**-alpha gene expression in human rheumatoid synoviocytes and normal monocytes by in situ hybridization.
MacNaul KL; Hutchinson NI; Parsons JN; Bayne EK; Tocci MJ
Department of Molecular Immunology, Merck Sharp and Dohme Research

Laboratories, Rahway, NJ 07065.
J Immunol (UNITED STATES) Dec 15 **1990**, 145 (12) p4154-66, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human IL-1 alpha, IL-1 beta, and TNF-alpha mRNA expression was examined in peripheral blood monocytes (PBM) from normal individuals and in primary synoviocytes isolated from patients with rheumatoid **arthritis** by Northern blot and in situ hybridization. Cells cultured in the presence or absence of LPS were analyzed using in vitro synthesized 35S-labeled sense or antisense RNA probes to determine the relative abundance and the cell type expressing each of the mRNA for these potent inflammatory mediators. The results indicated that 72% of the LPS-stimulated PBM expressed detectable levels of IL-1 alpha mRNA, 89% IL-1 beta mRNA, and 10% TNF-alpha transcripts. Thus, the majority of activated PBM produced both IL-1 alpha and IL-1 beta. Experiments combining immunofluorescence for IL-1 beta protein with in situ hybridization for TNF-alpha mRNA demonstrated that monocytes expressing TNF-alpha mRNA also produced IL-1 beta. Primary synoviocytes from four patients with RA were also examined for the mRNA expression of each cytokine. Northern blot analyses of total RNA isolated from 0 to 72 h after LPS- or mock-stimulation showed that IL-1 beta mRNA was the most abundantly expressed, followed by TNF-alpha. In situ hybridization revealed that IL-1 beta and TNF-alpha transcripts were detected exclusively in synovial tissue macrophages. IL-1 alpha mRNA was not detected in these cultures by either method.

1/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

07553650 91072650
Cytokines in chronic inflammatory **arthritis**. V. Mutual antagonism between interferon-gamma and **tumor** **necrosis** **factor**-alpha on HLA-DR expression, proliferation, collagenase production, and granulocyte macrophage colony-stimulating factor production by rheumatoid **arthritis** synoviocytes.
Alvaro-Gracia JM; Zvaifler NJ; Firestein GS
Department of Medicine, University of California, San Diego 92103.
J Clin Invest (UNITED STATES) Dec **1990**, 86 (6) p1790-8, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: AR-14916, AR, NIAMS; AR-39576, AR, NIAMS; CA-09174, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effects of a broad array of cytokines, individually and in combination, were determined on separate functions (proliferation, collagenase production, and granulocyte macrophage colony-stimulating factor [GM-CSF] production) and phenotype (expression of class II MHC antigens) of cultured fibroblast-like RA synoviocytes. The following recombinant cytokines were used: IL-1 beta, IL-2, IL-3, IL-4, IFN-gamma, tumor necrosis factor (TNF)-alpha, GM-CSF, and macrophage colony-stimulating factor (M-CSF). Only IFN-gamma induced HLA-DR (but not HLA-DQ) expression. TNF-alpha inhibited IFN-gamma-mediated HLA-DR expression (46.7 +/- 4.1% inhibition) and HLA-DR mRNA accumulation. This inhibitory effect was also observed in osteoarthritis synoviocytes. Only TNF-alpha and IL-1 increased synoviocyte proliferation (stimulation index 3.60 +/- 1.03 and 2.31 +/- 0.46, respectively). IFN-gamma (but none of the other cytokines) inhibited TNF-alpha-induced proliferation (70 +/- 14% inhibition) without affecting the activity of IL-1. Only IL-1 beta and TNF-alpha induced collagenase production (from less than 0.10 U/ml to 1.10 +/- 0.15 and 0.72 +/- 0.24, respectively). IFN-gamma decreased TNF-alpha-mediated collagenase production (69 +/- 19% inhibition) and GM-CSF production but had no effect on the action of IL-1. These data demonstrate mutual antagonism between IFN-gamma and TNF-alpha on fibroblast-like synoviocytes and suggest a novel homeostatic control mechanism that might be defective in RA where very little IFN-gamma is produced.

1/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

07536097 91055097
Cytokine regulation of colony-stimulating factor production in cultured human synovial fibroblasts: I. Induction of GM-CSF and G-CSF production by interleukin-1 and **tumor** **necrosis** **factor**.
Leizer T; Cebon J; Layton JE; Hamilton JA
Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia.
Blood (UNITED STATES) Nov 15 **1990**, 76 (10) p1989-96, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF), induce a dose-dependent production of both granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte CSF (G-CSF) in cultured human synovial cells, as measured by immunoassay. With IL-1, significant levels of both CSFs were first detected within 6 to 12 hours, with a maximum reached 24 to 48 hours after commencement of stimulation. A synergistic effect was detected between IL-1 and TNF in production of both CSFs in these cells. No evidence was obtained for the IL-1-induced effect to be mediated by induction of endogenous TNF nor for the TNF-induced stimulation to involve IL-1. IL-1-stimulated synovial cells were shown to secrete biologically active GM-CSF and G-CSF, which were specifically inhibited by their respective monoclonal antibodies. The transcription inhibitor, actinomycin D, and protein synthesis inhibitor, cycloheximide, inhibited the increase in GM-CSF and G-CSF production induced by IL-1 and TNF. Finally, other cytokines, IL-3, interferon gamma (IFN gamma), IL-2, platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and transforming growth factor alpha (TGF alpha), failed to stimulate either GM-CSF or G-CSF production, whether alone or in the presence of IL-1. These results suggest that cytokine-stimulated synovial fibroblasts may be a major source of intraarticular CSF production in the joints of patients with inflammatory **arthritis** ; as a result, monocyte/macrophages and granulocytes may be activated, leading to perpetuation of the inflammation and destructive events occurring in these lesions.

1/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

07534328 91053328
Tumour **necrosis** **factor** in serum and synovial fluid of patients with active and severe rheumatoid **arthritis**.
Tetta C; Camussi G; Modena V; Di Vittorio C; Baglioni C
Laboratorio di Immunopatologia, Universita di Torino, Italy.
Ann Rheum Dis (ENGLAND) Sep **1990**, 49 (9) p665-7, ISSN 0003-4967 Journal Code: 62W
Contract/Grant No.: CA-29895, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Fifteen serum samples and 29 synovial fluids of patients with rheumatoid **arthritis** (RA) were examined for the presence of tumour necrosis factor (TNF). The assay for TNF was based on the cytotoxic activity of this cytokine for human melanoma cells in tissue culture. High concentrations of TNF were found in serum samples of patients with severe RA, who had increased erythrocyte sedimentation rate and serum alpha 2 macroglobulin, but decreased haemoglobin and serum iron concentrations. Tumour necrosis factor was also found in the synovial fluid of 16 out of 29 patients. High TNF concentrations were found in fluids with greater than 10(10) leucocytes/l. Tumour necrosis factor was not detected in the serum of normal subjects or in synovial fluid of patients with osteoarthritis. A mediator of inflammation, such as TNF, may contribute to the severity of RA.

1/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

07490157 91009157

The effect of recombinant **tumor** **necrosis** **factor**-alpha on superoxide and metalloproteinase production by synovial cells and chondrocytes.

Ahmadzadeh N; Shingu M; Nobunaga M
Department of Internal Medicine, Kyushu University, Beppu, Japan.

Clin Exp Rheumatol (ITALY) Jul-Aug **1990**, 8 (4) p387-91, ISSN 0392-856X Journal Code: DFA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We studied the effect of recombinant tumor necrosis factor-alpha (rTNF-alpha) on the production of superoxide and metalloproteinase by rheumatoid synovial cells or osteoarthritis chondrocytes. rTNF-alpha significantly inhibited superoxide generation by osteoarthritis chondrocytes and rheumatoid synovial cells at a concentration of 23 U/ml. On the other hand, rTNF-alpha at a concentration of 1500 U/ml significantly enhanced superoxide production by rheumatoid synovial cells, osteoarthritis synovial cells and osteoarthritis chondrocytes, respectively. Metalloproteinase released by rheumatoid synovial cells and chondrocytes derived from osteoarthritis patients were stimulated by rTNF-alpha at a concentration of 94 U/ml. rTNF-alpha at the highest concentration (15000 U/ml) significantly inhibited metalloproteinase release by rheumatoid synovial cells. The enhancing effect of rTNF-alpha at higher concentrations on superoxide production by rheumatoid synovial cells and osteoarthritis chondrocytes was time dependent. These results suggest that rTNF-alpha has a biphasic effect on superoxide and metalloproteinase production, and hence may play an important role in the pathogenesis of inflammatory joint diseases.

1/3,AB/25

07439495 90346495

Effects of associated cytokines (IL-1, **TNF**-alpha, IFN-gamma and TGF-beta) on collagen and glycosaminoglycan production by cultured human synovial cells.

Daireaux M; Redini F; Loyau G; Pujol JP
Laboratoire de Biochimie du Tissu Conjonctif, CHU Cote de Nacre, Caen, France.

Int J Tissue React (SWITZERLAND) **1990**, 12 (1) p21-31, ISSN 0250-0868 Journal Code: GTG
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The production of collagen and glycosaminoglycans (GAG) was studied in cultured human synovial cells exposed to four cytokines, alone or in dual combination, namely interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma) and transforming growth factor-beta (TGF-beta). Among these cytokines, only TGF-beta (0.1-10 ng/ml) induced a significant and dose-dependent increase of collagen synthesis in a 24-h incubation. This effect was reversed when the factor was associated with either IL-1 beta (100-500 pg/ml), TNF-alpha (1-100 ng/ml) or IFN-gamma (100 U/ml). Except IFN-gamma which clearly inhibits the collagen production, the other cytokines IL-1 and TNF-alpha were not very effective when tested separately, although they generally induced a small reduction in collagen amount. IL-1 beta and TNF-alpha were found to be more efficient than TGF-beta in stimulating the production of GAG by the synovial cells. IFN-gamma exerted an antagonistic effect on the TGF-beta-induced stimulation of GAG synthesis. TNF-alpha and IL-1 beta were shown to have an additive effect on that production. The results indicate that interactions between cytokines present in the inflamed synovial tissue may modulate their respective actions and thus introduce differentials in their effect on collagen and GAG metabolism which are responsible for the alterations of synovial extracellular matrix in rheumatoid **arthritis**.

1/3,AB/26

07407981 90314981

Elevated substance P and accelerated cartilage degradation in rabbit

knees injected with interleukin-1 and **tumor** **necrosis** **factor**.
O'Byrne EM; Blancuzzi V; Wilson DE; Wong M; Jeng AY
Research Department, Ciba-Geigy Corporation, Summit, New Jersey 07901.
Arthritis Rheum (UNITED STATES) Jul **1990**, 33 (7) p1023-8, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cytokines, interleukin-1 (IL-1), tumor necrosis factor alpha, and the neurotransmitter, substance P, have been implicated in the pathogenesis of **arthritis** because they stimulate synovial cells to secrete prostaglandin E2 and collagenase in vitro. We investigated in vivo changes in intraarticular substance P and the degradation of cartilage proteoglycan in response to intraarticular cytokine injections in rabbits. Twenty-four hours after a single injection of 10 ng, 30 ng, or 100 ng of recombinant human IL-1 alpha (rHuIL-1 alpha) per joint, the mean +/- SEM levels of substance P detected in the cell-free joint lavage fluid were 250 +/- 67 fmoles, 480 +/- 60 fmoles, and 530 +/- 130 fmoles (n = 4-5), respectively. The level of substance P in the contralateral knees injected with diluent was 58 +/- 8 fmoles (n = 12). The level of substance P had increased by 2 hours after IL-1 injection and remained elevated in the joint 48 hours after injection. Cytokine-induced proteoglycan depletion was also time- and dose-dependent. Proteoglycan concentrations in articular cartilage dissected from the weight-bearing condyles were calculated as the ratio of sulfated glycosaminoglycan measured using 1,9-dimethylmethylene blue: hydroxyproline. After 48 hours, 10 ng, 30 ng, or 100 ng of rHuIL-1 alpha per joint decreased proteoglycan levels by 9 +/- 4%, 14 +/- 4%, and 21 +/- 3% (n = 8), respectively. Likewise, the injection of recombinant human tumor necrosis factor alpha induced depletion of intraarticular substance P and cartilage proteoglycan.

1/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

07334264 90241264
Mononuclear cells enhance prostaglandin E2 production of polymorphonuclear leukocytes via **tumor** **necrosis** **factor** alpha.
Akama H; Ichikawa Y; Matsushita Y; Shinozawa T; Homma M
Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.
Biochem Biophys Res Commun (UNITED STATES) Apr 30 **1990**, 168 (2) p857-62, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To clarify the interactions between mononuclear cells and polymorphonuclear leukocytes, and to identify the cytokine(s) that mediate the interaction, the effects of a culture supernatant of LPS-stimulated mononuclear cells on production of arachidonic acid metabolites of polymorphonuclear cells were studied. The culture supernatant of LPS-stimulated mononuclear cells increased production of prostaglandin E2 of polymorphonuclear cells. TNF alpha, but not IL-1, IL-2, IL-6, or IFN gamma, enhanced the prostaglandin E2 production when added in vitro. Additionally, an anti-rTNF alpha monoclonal antibody inhibited the stimulating activity of the culture supernatants. TNF alpha, produced by mononuclear cells, appears to play an important role in the development of inflammation, such as rheumatoid **arthritis**, by enhancing the arachidonic acid metabolism of the polymorphonuclear cells.

1/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

07322035 90229035
Conservation of the central MHC genome: PFGE mapping and RFLP analysis of complement, HSP70, and **TNF** genes in the goat.
Cameron PU; Tabarias HA; Pulendran B; Robinson W; Dawkins RL
Department of Clinical Immunology, Royal Perth Hospital, Queen Elizabeth II Medical Centre, Western Australia.
Immunogenetics (UNITED STATES) **1990**, 31 (4) p253-64, ISSN 0093-7711 Journal Code: GI4

Languages: ENGLISH
Document type: JOURNAL ARTICLE
A degree of conservation of the genes located between class II and class I [central major histocompatibility complex (MHC) genes] is apparent among mammalian species including primates and the mouse. Few others have been analyzed. The caprine MHC is of particular interest, since it has recently been observed that susceptibility to a lentivirus-induced polyarthritis (caprine **arthritis**) segregates with serologically defined MHC class I antigens. This **arthritis** resembles, in a number of respects, rheumatoid **arthritis** in man. Human cDNA probes were used to examine the caprine central MHC and class I and II genes by restriction fragment length polymorphism (RFLP) and by pulsed field gel electrophoresis (PFGE) in order to define the polymorphism and linkage of central MHC genes to class I and class II genes. An outbred population of dairy goats (Saanen, British Alpine, Anglo Nubian, and Toggenberg) was examined for class I and class II RFLPs. Both regions were found to be highly polymorphic. The number of fragments hybridizing to an HLA-B7 probe after Eco RI, Bam HI, Bgl II, or Hind III digestion suggests there may be 10-13 class I genes. The degree of polymorphism was comparable to that reported in the mouse. Limited polymorphism was found in the central MHC genes. The caprine C4 and CYP21 genes were duplicated and demonstrated RFLP with Bam HI, Hind III, Eco RV, and Taq I. An infrequent Taq I C2 polymorphism was found. PFGE revealed substantial conservation of both the order and linkage of the central MHC genes when compared with mouse and man. C4, C2, CYP21, HSP70, and tumor necrosis factor (TNF) genes are all located within 800 kilobase (kb) of the class I loci. Distant from the class I region, the C4, C2, and CYP21 genes are linked on a short genomic segment (180 kb Not I and 190 kb Pvu I fragments). HSP70 cohybridizes with the complement genes on a 380 kb Mlu I fragment. Linkage of HSP70, TNF, and class I genes was found on a single Not I fragment (610 kb). TNF and class I cohybridize on Pvu I (730 kb) and Not I (610 kb) fragments. Conservation of a similar central MHC genomic structure across species argues for functional interaction between the central MHC genes. We postulate selection for these central MHC genes through their role as non antigen-specific regulators of immune response.

1/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

07319429 90226429
Effects of **tumor** **necrosis** **factor** alpha and beta on resorption of human articular cartilage and production of plasminogen activator by human articular chondrocytes.
Campbell IK; Piccoli DS; Roberts MJ; Muirden KD; Hamilton JA
Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia.
Arthritis Rheum (UNITED STATES) Apr **1990**, 33 (4) p542-52, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We examined the effects of recombinant human tumor necrosis factor (TNF) on human articular cartilage and chondrocytes in culture. Both TNF alpha and TNF beta stimulated cartilage matrix breakdown during prolonged culture and elevated the levels of plasminogen activator (PA) activity in both the supernatants and cell layers of cultured chondrocytes. Characterization of the PA activities by immunochemistry and by zymography following gel electrophoresis indicated that human chondrocytes produce both urokinase-type PA and tissue-type PA in response to TNF. The addition of both interleukin-1 and TNF alpha or TNF beta to chondrocyte cultures demonstrated a synergism between these cytokines in the generation of PA activity in the culture supernatants and cell layers. Our results suggest that both activated lymphocytes and monocytes may contribute to the cartilage destruction of inflammatory **arthritis** through their stimulation of chondrocytes with TNF beta and TNF alpha, respectively. Since PA is the only neutral proteinase reported to be elevated in TNF-stimulated chondrocyte cultures, it could have an important role in TNF-mediated cartilage destruction.

1/3,AB/30
DIALOG(R)File 155:MEDLINE(R)

07274497 90181497
Stimulation of human chondrocyte prostaglandin E2 production by recombinant human interleukin-1 and **tumour** **necrosis** **factor**.
Campbell IK; Piccoli DS; Hamilton JA
University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Parkville, Australia.
Biochim Biophys Acta (NETHERLANDS) Mar 9 **1990**, 1051 (3) p310-8, ISSN 0006-3002 Journal Code: AOW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this study we have examined the effects of recombinant cytokine preparations on the production of prostaglandin E2 (PGE2) by human articular chondrocytes in both chondrocyte monolayer and cartilage organ cultures. The cytokines chosen for this study included only those reported to be present in rheumatoid synovial fluids and which therefore could conceivably play a role in chondrocyte activation in inflammatory **arthritis**. Of the cytokines tested, interleukin-1 (IL-1; alpha and beta forms) consistently induced the highest levels of PGE2 production followed, to a lesser extent, by tumour necrosis factor (TNF; alpha and beta forms). The IL-1s were effective at concentrations 2-3 orders of magnitude less than the TNFs, with each cytokine demonstrating a dose-dependent increase in PGE2 synthesis for the two culture procedures. The increased PGE2 production by the chondrocytes exhibited a lag phase of 4-8 h following the addition of the IL-1 or TNF and was inhibited by actinomycin D and cycloheximide, indicating a requirement for de novo RNA and protein synthesis, respectively. Our results suggest that IL-1 may be the key cytokine involved in modulating chondrocyte PGE2 production in inflammatory **arthritis** ; they further extend the list of human chondrocyte responses which are affected by both IL-1 and TNF.

1/3,AB/31
DIALOG(R)File 155:MEDLINE(R)

07257521 90164521
Tumor **necrosis** **factor** alpha and interleukin 1 beta in synovial fluid of infants and children with suppurative **arthritis**.
Saez-Llorens X; Mustafa MM; Ramilo O; Fink C; Beutler B; Nelson JD
Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas.
Am J Dis Child (UNITED STATES) Mar **1990**, 144 (3) p353-6, ISSN 0002-922X Journal Code: 3GS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor necrosis factor alpha and interleukin 1 beta concentrations were measured in synovial fluid of 24 infants and children with diagnoses of suppurative **arthritis** (n = 16) and other kinds of **arthritis** (n = 8). Large concentrations of tumor necrosis factor alpha (range, 100 to 85,000 pg/mL) were found in 12 (75%) of 16 patients with bacterial infection and in none of the patients with noninfectious origins. Large concentrations of interleukin 1 beta (greater than 200 pg/mL) were found in 15 (94%) of 16 patients with bacterial infection and in none of the other patients. In the latter group, small concentrations of interleukin 1 (range, 40 to 120 pg/mL) were present in 5 (63%) of 8 patients. Serum samples obtained simultaneously were negative for both cytokines. Tumor necrosis factor alpha and interleukin 1 beta concentrations correlated significantly and with leukocyte counts in synovial fluid. We conclude that large concentrations of tumor necrosis factor alpha and interleukin 1 beta are produced locally in patients with suppurative **arthritis** and they may be potentially useful in differentiating this condition from other kinds of **arthritis**.

File 351:DERWENT WPI 1981-1996/UD=9629;UA=9625;UM=9617

S1 9 ((TNF?/TI OR (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?/TI) AND ARTHRITIS) AND PY=1990:1991PB
?Ds1/3,ab/all

Discoordinate expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases-1 in rheumatoid human synovial fibroblasts. Synergistic effects of interleukin-1 and **tumor** **necrosis** **factor** -alpha on stromelysin expression.

MacNaul KL; Chartrain N; Lark M; Tocci MJ; Hutchinson NI
Department of Molecular Immunology, Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065.

J Biol Chem (UNITED STATES) Oct 5 **1990**, 265 (28) p17238-45, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Primary and passaged human synovial fibroblasts isolated from rheumatoid pannus were treated with recombinant interleukin-1 (IL-1) alpha or beta, tumor necrosis factor-alpha (TNF), or phorbol myristate acetate (PMA) to determine the effects of these stimuli on the relative expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases (TIMP). The steady-state mRNA levels for these genes and glyceraldehyde-3-phosphate dehydrogenase were determined on Northern blots. Immunoblot analyses of the conditioned media using monoclonal antibodies generated against recombinant human stromelysin, collagenase, or TIMP showed that protein levels reflected the corresponding steady-state mRNA levels. The results revealed that 1) stromelysin and collagenase were not always coordinately expressed; 2) IL-1 was more potent than TNF or PMA in the induction of stromelysin expression; 3) neither IL-1 nor TNF significantly affected TIMP expression; 4) PMA induced both metalloproteinase and TIMP expression; and 5) the combination of IL-1 plus TNF had a synergistic effect on stromelysin expression. Dose response and time course experiments demonstrated that the synergistic effect of IL-1 plus TNF occurred at saturating concentrations of each cytokine and lasted for 7 days. In summary, the ability of IL-1 and TNF to preferentially induce stromelysin and collagenase expression, versus TIMP, may define a pivotal role for these cytokines in the pathogenesis of rheumatoid **arthritis**.

1/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

07485233 91004233
A nonsecretable cell surface mutant of **tumor** **necrosis** **factor** (**TNF**) kills by cell-to-cell contact.

Perez C; Albert I; DeFay K; Zachariades N; Gooding L; Kriegler M
Department of Molecular Biology, Cetus Corporation, Emeryville, California 94608.

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Document type: JOURNAL ARTICLE

In addition to the induction of tumor regression, tumor necrosis factor (TNF) has been implicated as the causative agent in a number of pathologies, including cachexia, septic shock, rheumatoid **arthritis**, autoimmunity, and induction of HIV expression. We propose that this complex physiology might be manifest by different forms of TNF: the 17 kd secretory component, the 26 kd transmembrane form, or both. To determine whether the 26 kd form of TNF was biologically active and whether its biology differed from that of the secretory component, we generated uncleavable and solely secretable mutants of TNF and studied their biological activities. We found that an uncleavable mutant of the 26 kd cell surface transmembrane form of TNF kills tumor cells and virus-infected cells by cell-to-cell contact, and that TNF need not be internalized by its target to kill. Thus, the 26 kd integral transmembrane form of TNF may function in vivo to kill tumor cells and other targets locally in contrast to the systemic bioactivity of the secretory component.

1/3,AB/24
DIALOG(R)File 155:MEDLINE(R)

07467576 90374576

1/3,AB/1
DIALOG(R)File 351:DERWENT WPI

008821109 WPI Acc No: 91-325122/44
XRAM Acc No: C91-140447
New phenyl-cycloalkane and -cycloalkene derivs. - inhibit **TNF** and phospho-diesterase prodn. used for treating asthma, cerebrovascular disorders, allergic and inflammatory diseases etc.
Patent Assignee: (SMIK) SMITHKLINE BEECHAM CORP; (SMIK) SMITHKLINE BEECHAM PHARMA GMBH; (SMIK) SMITHKLINE BEECHAM
Author (Inventor): CHRISTENSEN S B; MASCHLER H; CHRISTENSE S B
Patent Family:

CC Number	Kind	Date	Week	
WO 9115451	A	911017	9144	(Basic)
AU 9176709	A	911030	9205	
EP 523138	A1	930120	9303	
JP 6500071	W	940106	9406	
US 5362915	A	941108	9444	

Priority Data (CC No Date): GB 907762 (900405)
Applications (CC,No,Date): WO 91EP637 (910402); US 934546 (921002); EP 91907473 (910402); WO 91EP637 (910402); JP 91506839 (910402); WO 91EP637 (910402)
Abstract (Basic): WO 9115451
Phenyl-cycloalkanes and -cycloalkenes of formula (I) or their salts are new. R1 = Me or Et opt. substd. by 1-3F; X = O or S(O)s; s = 0-2; R2 = 4-6C cyclic alkyl opt. substd. by 1-3 Me or 1 Et; -Ch2-cyclopentyl, -CH2-cyclopropyl, 3-tetrahydrofuranyl, 1-7C alkyl, Me or Et substd. by 1-3F; -(CH2)nCOO(CH2)gCH3 or (CH2)nO(Ch2)gCH3; n = 2-4; g = 0-2; R3 = a gp. of formula (a); R4, R5 = H, or R4+R5 = a bond; Y = C=P. C=S or Ch-R6; R6 = H, Oh, 1-6C alkoxy or 1-6C thioalkoxy; m, r = 0-4; m+r = 2-4; provided that when R1 = Me, X = O, R2 = Me or cyclopentyl, R3 = cyclopent-1,2-ene-3-one.
USE - (I) have PDE IV activity and are useful in treating asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophillic granuloma psoriasis, rheumatoid **arthritis** etc. (I) are also useful in treating (esp. cerebral) vascular and neuronal disorders cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type etc. and in the prophylaxis of cerebral ischaemia due to cardiac arrest, stroke, surgery and/or during childbirth intermittent claudication. (I) also inhibit prodn. of TNF which is implicated in e.g. rheumatoid **arthritis**, gouty **arthritis**, AIDS, pyresis and ulcerative colitis. Daily dosage is 0.001-40 mg/kg, parenterally.
@(47pp Dwg.No.0/0)@
Abstract (US): 9444 US 5362915 A
Cpds. of formula (I) or its pharmaceutically acceptable salt is new. R1 is CH3 or CH2CH3 opt. substd. by 1-3F; X is O or S(O)s; s = 0-2; R2 is 4C cyclic alkyl opt. substd. by 1-3 CH3 or 1 CH2CH3; CH2-cyclopentyl; CH2-cyclopropyl, 3-tetrahydrofuranyl, 1-7C alkyl, CH3 or CH2CH3 substd. by 1-3F; (CH2)nCOO-(CH2)gCH3 or (CH2nO(CH2)gCH3 where n is 2-4 and g is 0-2; R3 is gp. (a); R4, 5 are each H or R4+R5 is a bond; B is C=O, C=S, or CH-R6; R6 is H, OH, 1-6C alkoxy or 1-6C thioalkoxy; m, r are each 0-4 where m+r is 2-4; provided that when R1 is CH3, X is O, and R2 is CH3 or cyclopentyl, R3 is not cyclopent-1,2-ene-3-one. Pref. R1 is CH3, X is O, and R is 4-6C cycloalkyl.
USE/ADVANTAGE - As PDE-IV inhibitors in medicinal compsns. Protective effect against cerebral metabolic inhibition. Improves data acquisition or retrieval.
Dwg.0/0

1/3,AB/2
DIALOG(R)File 351:DERWENT WPI

008791565 WPI Acc No: 91-295580/40
XRAM Acc No: C91-127783
New neutrophil stimulating peptide(s) derived from human **TNF** - useful for treating depressed neutrophil function in e.g. AIDS and cancer, and inflammatory syndrome in e.g. rheumatoid **arthritis**;

TUMOUR NECROSIS FACTOR ACQUIRE IMMUNE DEFICIENT SYNDROME
Patent Assignee: (PEPT-) PEPTIDE TECHNOLOGY LTD; (PEPT-) PEPTIDE TECHN LTD
Author (Inventor): FERRANTE A; RATHJEN D A
Patent Family:

CC Number	Kind	Date	Week	
WO 9113908	A	910919	9140	(Basic)
AU 9174762	A	911010	9201	
EP 519976	A1	921230	9301	
JP 5506850	W	931007	9345	
AU 642487	B	931021	9349	

Priority Data (CC No Date): AU 909065 (900312)
Applications (CC,No,Date): AU 9174762 (910312); EP 91905955 (910312); WO 91AU86 (910312); JP 91505600 (910312); WO 91AU86 (910312)
Abstract (Basic): WO 9113908 A

A peptide (I) having the approximate amino acid sequence of amino acids 54-94 of the sequence given in the specification is claimed. (I) is capable of priming neutrophils to produce superoxide and an enhanced respiratory burst after treatment with N-formyl-L-methionyl-L -leucyl-L-phenylalanine (2). (I) pref. corresponds to amino acids 52-94, 54-68, 73-94 or 70-80 of the sequence in the specification.

The peptides are synthesised by Fmoc-polyamide solid phase peptide synthesis, using polydimethylacrylamide gel on kieselguhr support with 4-hydroxymethylphenoxyacetic acid as the functionalised linker. The C-terminal amino acid is attached to the solid support by a DCC/DMAP-mediated symmetrical-anhydride esterification. Fmoc-gps. are removed by piperidine/DMF wash and peptide bonds are formed via pentafluorophenyl active esters or directly by Castro's reagent.

USE/ADVANTAGE - (I), derived from human TNF, is used to treat depressed neutrophil function in e.g. AIDS and cancer and to treat an inflammatory syndrome e.g. rheumatoid **arthritis** and adult respiratory distress syndrome (all claimed). @(23pp Dwg.No.0/5)

1/3,AB/3
DIALOG(R)File 351:DERWENT WPI

008733943 WPI Acc No: 91-237959/32
XRAM Acc No: C91-103495
New ureido derivs. of poly-4-amino-2-carboxy-1-methylpyrrole cpds. - used as angiogenesis inhibitors in treating chronic inflammation and tumour growth, etc., and as **TNF**-alpha inhibitors in treating AIDS, etc.
Patent Assignee: (FARM) FARMITALIA ERBA SRL CARLO; (PHAA) PHARMACIA SPA
Author (Inventor): BIASOLI G; CIOMEI M; GRANDI M; MONGELLI N; PAIO A
Patent Family:

CC Number	Kind	Date	Week	
WO 9110649	A	910725	9132	(Basic)
AU 9170599	A	910805	9145	
PT 96455	A	911015	9146	
FI 9104251	A	910909	9149	
ZA 9100177	A	911030	9149	
CS 9100056	A	911015	9150	
EP 462258	A	911227	9201	
NO 9103572	A	910910	9203	
CN 1053230	A	910724	9217	
JP 4504426	W	920806	9238	
NZ 236707	A	921028	9301	
HU T61280	T	921230	9306	
US 5260329	A	931109	9346	
AU 647446	B	940324	9417	
NO 176274	B	941128	9502	
US 5420296	A	950530	9527	
IL 96875	A	950330	9530	
EP 462258	B1	951220	9604	
DE 69115570	E	960201	9610	
ES 2084153	T3	960501	9625	

Priority Data (CC No Date): GB 90644 (900111)
Applications (CC,No,Date): EP 91902204 (910107); ZA 91177 (910109); EP 91902204 (910107); JP 91502425 (910107); WO 91EP14 (910107); NZ 236707 (910107); HU 912923 (910107); WO 91EP14 (910107); WO 91EP14 (910107); US 752577 (910909); AU 9170599 (910107); WO 91EP14 (910107); NO 913572

(910910); US 752577 (910909); US 66583 (930525); IL 96875 (910103); EP 91902204 (910107); WO 91EP14 (910107); DE 615570 (910107); EP 91902204 (910107); WO 91EP14 (910107)

Abstract (Basic): WO 9110649 A

Ureido derivatives of poly-4-amino-2-carboxy-1-methyl pyrrole compounds of formula (I) and their salts are new. m, n = 1-3. W = O or S. B = (un)saturated carbocyclic or condensed carbocyclic ring substituted by at least 1 acid group; an (un)saturated heteromonocyclic or heterobicyclic ring containing at least 1 of N, O and S and substituted by at least 1 acid group; a pyranyl or furanyl sugar residue substituted by at least 1 acid group; or -CH2-(CHA)r-CH2A. A = an acid group. r = 0, 1 or 2.

18 compounds are specifically claimed including 8,8'-(carbonyl-bis(imino-N-methyl-4, 2-pyrrolecarbonyl-imino-(N-methyl-4, 2-pyrrole)carbonylamino))bis1,3-naphthalene di-sulphonic acid). Also claimed is the preparation of (I) which comprises reacting the corresponding amino compound with a ketone or thioketone compound containing leaving groups.

USE/ADVANTAGE - As angiogenesis inhibitors (claimed) which are used for treating chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid **arthritis** and tumour growth. (I) are also used to treat diseases in which TNF-alpha has a detrimental role (claimed), including cachexia, septic shock, graft versus host disease, AIDS and cerebral malaria. The dose is 0.5-300 mg pro dose 1-4 times a day. @(32pp Dwg.No.0/0)@

Abstract (US): 9527 US 5420296 A

Poly-4-amino-2-carboxy-1-methyl pyrrole derivs. of formula (II) and their salts are new. In (I) n is 1-3, B is phenyl, naphthyl, tetrahydropyranyl, tetrahydrofuranyl, quinoline or pyranyl- or furanyl sugar residue opt. substd. by 1-3 of sulphonic, sulphuric, sulphamic, sulphinic, phosphoric, phosphonic, phosphamic or carboxylic acid gps.

4 Cpds. are specifically claimed including 8-(amino-N-methyl-4,2-pyrrole -carbonyl-imino-(N-methyl-4, 2-pyrrole)carbonylimino) (1,5-naphthalen-disulphonic acid disodium salt) hydrochloride.

USE - (I) are angiotensin inhibitors and TNF alpha-neutralisers used to treat e.g. cachexia, septic shock, graft vs. host disease, AIDS, cerebral malaria, rheumatoid **arthritis**, diabetic retinopathy, psoriasis etc.

Dwg.0/0 9346 US 5260329 A

Polyamino carboxymethyl cpds. of formula (I) and salts are new. Each of M and N is an integer of 1-3; W is O or S; each of the B groups, which are the same, are a -CH2(-CHA)rCH2A group, where each A group is acid gp. independently selected from sulphonic, sulphuric, sulphamic, sulphonic, phosphoric, phosphonic, phosphamic and carboxylic acid groups, and r is 0, 1 or 2

Abstract (EP): 9604 EP 462258 B

A compound of formula (I) wherein each of m, n are 1-3; W is oxygen or sulphur; each of the B groups, which are the same, is a) a phenyl or naphthyl group substituted by one or more acid groups; b) a saturated or unsaturated, heteromonocyclic or heterobicyclic ring, containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur, substituted by one or more acid groups; c) a deoxy-D-glucose group substituted by one or more acid groups; or d) a -CH2(CHA)rCH2A group, wherein each A group, being the same or different, is an acid group and r is 0, 1 or 2; and wherein each of the above acid groups is independently chosen from sulfonic, sulfuric, sulfamic, sulfinic, phosphoric, phosphonic, phosphamic and carboxylic acid groups; and the pharmaceutically acceptable salts thereof. Dwg.0/0

1/3,AB/4

008583081 WPI Acc No: 91-087113/12
XRAM Acc No: C91-036996

Identification of proteins acting as **TNF** convertase inhibitors - comprises comparing conversion of pro-hormone contacted with convertase to that of pro-hormone in presence of test cpd

Patent Assignee: (CETU) CETUS ONCOLOGY CORP; (CETU) CETUS CORP

Author (Inventor): KRIEGLER M P; PEREZ C F; KRIEGLER M; PEREZ C
Patent Family:

CC Number	Kind	Date	Week	
WO 9102540	A	910307	9112	(Basic)
CA 2020700	A	910217	9118	
AU 9059400	A	910403	9125	
NO 9200593	A	920319	9224	
EP 491878	A1	920701	9227	
JP 4507044	W	921210	9304	
AU 9520474	A	951019	9549	

Priority Data (CC No Date): US 395253 (890816)
Applications (CC,No,Date): AU 9520474 (950602); AU 9059400 ( ); WO 90US3266 (900608); NO 92593 (920214); EP 90917939 (900608); WO 90US3266 (900608); JP 90509543 (900608); WO 90US3266 (900608)
Abstract (Basic): WO 9102540

Method for identifying prophylactics or therapeutics of diseases caused by a mature protein hormone or at least 1 lower mol. wt. species of the hormone, which are produced from a prohormone by convertase cleavage. The method comprises (a) contacting the prohormone with convertase, (b) measuring the conversion of the prohormone to the mature hormone or lower mol. wt. species, (c) repeating steps (a) and (b) and including the test molecule, (d) measuring the conversion of the prohormone and (e) comparing the amt. of conversion of the prohormone from steps (b) and (d).

The therapeutics and prophylactics themselves are also claimed. They inhibit or prevent the convertase from producing mature hormone, by competing with it for binding to the prohormone. The prohormone is pref. 26Kd tumour necrosis factor.

USE/ADVANTAGE - Those proteins or peptides identified as tumour necrosis factor convertase inhibitors are used to treat sepsis, AIDS and autoimmune diseases, esp. **arthritis** (claimed). @(43pp Dwg.No.0/3)@

1/3,AB/5
DIALOG(R)File 351:DERWENT WPI

008532492 WPI Acc No: 91-036576/05
XRAM Acc No: C91-015623
Use of diaryl fused imidazole derivatives - for inhibition of IL-1 and **TNF** prodn. in monocytes or macrophage(s) in treatment of rheumatoid **arthritis** etc.
Patent Assignee: (SMIK) SMITHKLINE BEECHAM CORP; (SMIK) SMITHKLINE BEECHAM
Author (Inventor): BADGER A M; BENDER P E; ESSER K M; GRISWOLD D E; HANNA N ; LEE J C; SIMON P L; VOTTA B J; LEE J; NABIL H; VOTTA J
Patent Family:

CC Number	Kind	Date	Week	
WO 9100092	A	910110	9105	(Basic)
EP 411754	A	910206	9106	
AU 9063551	A	910117	9117	
ZA 9004581	A	910626	9131	
JP 5503919	W	930624	9330	
US 5317019	A	940531	9421	

Priority Data (CC No Date): US 365349 (890613)
Applications (CC,No,Date): WO 90US3367 (900613); US 809484 (911212); EP 90306437 (900613); ZA 904581 (900613); JP 90512684 (900612); WO 90US3367 (900612)
Abstract (Basic): WO 9100092

Inhibition of IL-1 production is accomplished with compounds of formula (I). R1 = -CR4R5-CR6R7-, -CR5 = CR7-, -N = CR7-, -S(O)m- or -O- n = 0-2; One of R1 RO is 4-pyridyl or 4-alkyl-pyridine-2-yl and the other is: (a) Phenyl optionally monosubstituted by 1-3 alkylthio, alkyl-sulphinyl, alkenyl-thio, alkenyl-sulphinyl, 1-acyloxy-1-alkylthio, 1-2C alkoxy, halo, 1-4C alkyl, -S-S-Z1 (Z1 = Ph or 1-9C alkyl) or a group (II) (b) phenyl' independently disubstituted by 1-3C alkylthio, alkoxy, halo or alkyl; (c) phenyl where one substituent is alkylsulphinyl, alkenylthio, alkenylsulphinyl, alkenylthio or acyloxythio and the other is alkyl, halo or alkyl. (d) phenyl where both substituents are as the first one in C) or together they form methylenedioxy. t = 0 or 1; R2, R3, R4, R5, R6, R7, R8, R9 =

A pharmaceutical composition which comprises an antibody against human-alphatumour necrosis factor and an antilymphocyte antibody in admixture with one or more pharmaceutically acceptable carriers, excipients or diluents.

1/3,AB/7
DIALOG(R)File 351:DERWENT WPI

007927439 WPI Acc No: 89-192551/26
Related WPI Accession(s): 88-205301
XRAM Acc No: C89-085221
Use of 7-(oxoalkyl)-1,3-dialkyl xanthine cpds. - for inhibiting the activity of leukocyte derived cytokines such as interleukin-1 or **tumour** **necrosis** **factor**; OXOALKYL
Patent Assignee: (HMRI) HOECHST ROUSSEL PHARM INC; (UYVI-) UNIV VIRGINIA; (UYVI-) UNIV VIRGINIA PATENTS FOUND; (UYVI-) UNIV VIRGINIA ALUMNI PATENTS FOUND
Author (Inventor): MANDELL G L; NOVICK W J; SULLIVAN G W
Patent Family:

CC Number	Kind	Date	Week	
WO 8905145	A	890615	8926	(Basic)
AU 8928285	A	890705	8937	
EP 344288	A	891206	8949	
DK 8903919	A	890810	8950	
JP 2502542	W	900816	9039	
ZA 8909235	A	900926	9044	
US 4965271	A	901023	9045	
US 5096906	A	920317	9214	
AU 632466	B	930107	9308	
US 5196429	A	930323	9314	
AU 9335641	A	930603	9329	
IL 88656	A	930708	9335	
IL 102920	A	940530	9424	
IL 102921	A	940530	9424	
IL 102922	A	940530	9424	
AU 652094	B	940811	9435	
IL 102919	A	940826	9435	
EP 344288	B1	950215	9511	
CA 1334508	C	950221	9515	
DE 3853067	G	950323	9517	
EP 344288	A4	920115	9520	
JP 2507105	B2	960612	9628	

Priority Data (CC No Date): US 131785 (871211); US 947905 (861231); US 239761 (880902); US 508535 (900411); US 622138 (901205); US 131785 (861231); US 738096 (910730)
Applications (CC,No,Date): WO 88US4375 (881207); JP 89500674 (881207); WO 88US4375 (881207); EP 89900768 (881207); JP 89500674 (881207); ZA 889235 (881209); AU 8928285 (881207); US 131785 (871211); US 622138 (901205); AU 9335641 (930401); AU 8928285 ( ); IL 88656 (881211); IL 102920 (881211); IL 102921 (881211); IL 102922 (881211); AU 9335641 (930401); AU 8928285 ( ); IL 102919 (881211); WO 88US4375 (881207); EP 89900768 (881207); CA 585678 (881212); DE 3853067 (881207); WO 88US4375 (881207); EP 89900768 (881207); EP 89900768 (881207)
Abstract (Basic): WO 8905145 A

Inhibiting interleukin-1 activity, tumour necrosis factor activity and the activity of other lekocyte derived cytokines in a mammal comprises administering a 7-(oxoalkyl)-1,3-dialkyl xanthine of formula (I), where R1,R2= 2-6C alkyl, cycloaklyl or alkoxyalkyl or hydroxyalkyl other than 3-methyl-3-hydroxy butyl, 3-methyl-3-hydroxy pentyl or 4-methyl 4-hydroxy pentyl; A = a hydrocarbon gp. with up to 4C which can be substd. by a methyl gp. More specifically, (I) is 1,3-dibutyl 7-(Z-oxopropyl) xanthine (Ia).

USE - (I) are capable of modulating the effects of lekocyte derived cytokines on phagocytes such as polymorphonuclear leukocytes. They are capable of aiding chemotaxis. In addn., they can block adherence of cells. They can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear leukocytes. The cpds. can also modulate the effects of cytokines on degranulation in stimulated phagocytes. Conditions which can be treated or alleviated include e.g. sepsis,

spetic shock, endotoxic shock, adult respiratory distress, fever and myalgias due to infection, cachexia secondary to infection or malignancy or AIDS, rheumoatoid **arthritis**, gouty **arthritis**, osteoporosis, keloid formation, ulcerative colitis, fever due to central nervous system bleeding, glomerulonephritis, multiple sclerosis, Creutzfeld-Jacab disease, adverse reactions to dialysis, diabetes melitus and psoriasis. The cpds. can also enhance phagocyte activity in stored blood and blood prods. Dwg.0.7

Abstract (US): 9314 US 5196429 A

Treating an adverse condition in a mammal caused by HIV comprises admin. of a xanthine deriv. of formula (I). In the formula at least one of R1 and R3 is -(CH2)nC(OH)(R4)Me or -(CH2)pC(=O)R6; and the other is H or a 1-6C aliphatic gp. opt. interrupted by 2 oxygen atoms and opt. substd. by OH or oxo; R6 is 1-6C alkyl; p is 2-4; and R2 is 1-4C alkyl.

USE/ADVANTAGE - (I) inhibits interleukin; 1 tumour necrosis factor and other leukocyte derived cytokines even at low concns. inhibiting their effects on polymorphonuclear leukocyte and monocyte adherence, cell chemotaxis, respiratory (metabolic) burst and cell degranulation. They are also used to treat or alleviate e.g. endotoxic shock, rheumatoid **arthritis**, Crohns disease, glomerulonephritis etc.. Dosage is 0.1-25 mg/kg/day by i.v., p.o. or parenteral admin..

Dwg.0/12 9214 US 5096906

Treating a human to inhibit tissue injury accompanying inflammation resulting from leukocyte activity induced by cytokines produced in response to an inflammatory stimulus comprises administration of at least one cpd. of formula (I). In (I) at least one of R' and R3 is either (a) branched hydroxyalkyl gp. of formula (CH2)n-CR4OH-CH3 (where R4 is 1-3C alkyl) n is 2-5) the other R1 or R3 that is opt. present is H or an aliphatic hydrocarbon gp. R5 with upto 6C, whose carbon chain may be interrupted by up to 2 oxygen atoms or substd. with -OH or OXO gp. or (b) an oxoallyl gp. of formula R6-CO-(CH2)p (where R6 is 1-6C; p is 2-4) and R2 is 1-4C alkyl.

USE/ADVANTAGE - (I) is administered to human in an amt. sufficient to inhibit activity of human interleukin-1, human tumor necrosis factor or the activity of other human leukocyte-derived human cytokines on polymorpho-nuclear leukocytes or monocytes in the human to inhibit tissue injury. @(24pp)@ 9045 US 4965271

New treatment to inhibit tissue injury due to leucocyte-induced inflammation by cytokines comprises admin. a 7-(oxoalkyl)-1,3-dialkyl xanthine of formula (I). In (I), R1 and R2 are each 2-6C alkyl, cyclohexyl, alkoxy- or hydroxy-alkyl; A is 1-4C hydrocarbyl opt. susbtd. Me. Applicable to inhibition of IL-1, TNF, or other cytokines from leucocytes acting on polymorphonuclear leukocytes or monocytes.

Esp. cpd. is 1,3-dibutyl-7-(2-oxopropyl)xanthine.

(I) may be prepd. by e.g. reacting 1,3-dialkylxanthines of formula (III) with unsatd. methylketones of formula (IV).

USE - Treatment of inflammation, sepsis, septic and endotoxic shock, adult erspiratory syndrome, fever and cschexia of AIDS. Dose e.g. 0.1-25(1)mg/kg/day. @(17pp

Abstract (EP): 9511 EP 344288 B

Use of at least one compound of general formula (I) for preparing a medicament for alleviating a disease except psoriasis in a mammal mediated by interleukin-1 (L-1), tumour necrosis factor (TNF), or other leukocyte derived cytokines: in which R1 and R2 are the same or different and are selected from the group consisting of straight-chain or branched alkyl radicals with 2 to 6 carbon atoms, cyclohexyl, alkoxyalkyl and hydroxyalkyl radicals other than a 3-methyl-3-hydroxybutyl radical, 3-methyl-3- hydroxypentyl radical, or 4-methyl-4-hydroxypentyl radical, and A represents a hydrocarbon radical with up to 4 carbons atoms which can be substituted by a methyl group, with the proviso that A is not C2 to C4 when R2 is C2 to C4 and R1 is (II) wherein R4 is an alkyl group with 1 to 3 carbon atoms and n is an integer from 2 to 5, or R1 is an aliphatic hydrocarbon group R5 with up to 6 carbon atoms, whose carbon chain is interrupted by an oxygen atom or is substituted by a hydroxy group.

Dwg.0/7

1/3,AB/8

XRPX Acc No: N88-228559

Detection of **tumour** **necrosis** **factor** by immunoassay - useful for monitoring disease states, e.g. Kawasaki disease and bacterial infection

Patent Assignee: (TEIJ) TEIJIN KK

Author (Inventor): YONE K; SUZUKI J; TSUNEKAWA N; KATO A; NAKAMURA S; MASEGI T; KITAI K; ICHIKAWA Y

Patent Family:

CC Number	Kind	Date	Week	
EP 288088	A	881026	8843	(Basic)
JP 2001552	A	900105	9007	
US 5075236	A	911224	9203	
EP 288088	B1	940309	9410	
DE 3888224	G	940414	9416	

Priority Data (CC No Date): JP 87100010 (870424); JP 87162233 (870701); JP 87162234 (870701); JP 87268218 (871026); JP 87268219 (871026); JP 87166234 (870701); JP 88100186 (880425)

Applications (CC,No,Date): DE 3888224 (880425); EP 88106585 (880425); EP 88106585 (880425); US 186078 (880425); EP 88106585 (880425)

Abstract (Basic): EP 288088

Diseased condition of a subject may be determined by detecting a substance reactive with an anti-tumour necrosis factor (I) antibody in a body fluid sample. An immunoassay procedure using the (I) antibody is used. Typically the subject is a patient with Kawasaki disease or a bacterial infection. Also claimed is anti-human (I) monoclonal antibody which can neutralise the cytotoxic effect of human (I) on L929 cells. Monoclonal antibodies which recognise epitopes contd. in (i) the 7-37th aminoacids and (ii) the 113-127th aminoacids of the aminoacid sequence of human (I), are also new. Detection kits are also provided.

USE/ADVANTAGE - Any disease which shows abnormal (I) levels may be monitored. Other examples are autoimmune diseases (e.g. SLE and rheumatoid **arthritis**), chronic inflammatory diseases leg sarcoidosis and Crohn's disease), congenital and acquired immunodeficiencies, vascular inflammatory diseases e.g. disseminated iv. coagulation and graft versus host disease. The method is accurate and fast. @(19pp Dwg.No.0/6)@

Abstract (US): 9203 US 5075236

Diagnosis of Kawasaki disease comprises incubation of a body fluid sample with an anti-tumour necrosis factor antibody (opt. obtd. by monoclonal methods); and determination of the formation of the corresp. antigen-antibody complex, comparing the result with that obtd. using a body fluid sample from a healthy subject not having the disease.

USE - The process aids rapid clinical analysis and diagnosis. @(14pp)@

Abstract (EP): 9410 EP 288088 B

Diseased condition of a subject may be determined by detecting a substance reactive with an anti-tumour necrosis factor (I) antibody in a body fluid sample. An immunoassay procedure using the (I) antibody is used. Typically the subject is a patient with Kawasaki disease or a bacterial infection. Also claimed is anti-human (I) monoclonal antibody which can neutralise the cytotoxic effect of human (I) on L929 cells. Monoclonal antibodies which recognise epitopes contd. in (i) the 7-37th aminoacids and (ii) the 113-127th aminoacids of the aminoacid sequence of human (I), are also new. Detection kits are also provided.

USE/ADVANTAGE - Any disease which shows abnormal (I) levels may be monitored. Other examples are autoimmune diseases (e.g. SLE and rheumatoid **arthritis**), chronic inflammatory diseases leg sarcoidosis and Crohn's disease), congenital and acquired immunodeficiencies, vascular inflammatory diseases e.g. disseminated iv. coagulation and graft versus host disease. The method is accurate and fast.

007822634 WPI Acc No: 89-087746/12
Related WPI Accession(s): 90-350112; 91-045654; 92-374839
XRAM Acc No: C89-038816
Tumour **Necrosis** **Factor** inhibitory protein - isolated from urine and having ability to inhibit the binding of **TNF** to its receptors and its cytotoxic effect
Patent Assignee: (YEDA) YEDA RES & DEV CO LTD
Author (Inventor): ADERKA D; ENGELMANN H; RUBINSTEIN M; WALLACH D
Patent Family:

CC Number	Kind	Date	Week	
EP 308378	A	890322	8912	(Basic)
AU 8822068	A	890316	8924	
JP 2000200	A	900105	9007	
ZA 8806818	A	900131	9009	
EP 308378	B1	941130	9501	
DE 3852255	G	950112	9507	
ES 2067486	T3	950401	9520	
IL 83878	A	950731	9540	
US 5512544	A	960430	9623	

Priority Data (CC No Date): IL 83878 (870913); IL 90339 (890518); IL 98078 (910507)
Applications (CC,No,Date): EP 88830365 (880913); JP 88228307 (880912); ZA 886818 (880913); EP 88830365 (880913); DE 3852255 (880913); EP 88830365 (880913); EP 88830365 (880913); US 243092 (880912); US 524263 (900516); US 876828 (920430); US 879373 (920507)
Abstract (Basic): EP 308378 A

A Tumour Necrosis Factor (TNF) inhibitory protein, salts, Functional derivs. and active fractions and mixts. of any of these having the ability to inhibit (a) the binding of TNF to its receptors and (b) the cytotoxic effect of TNF are claimed.

Also claimed is A DNA molecule comprising the nucleotide sequence coding for the TNF inhibitory protein, a replicable expression vehicle contg. the DNA molecule and a host cell transformed with the replicable expression vehicle.

USE - The TNF inhibitory protein can be used for antagonising the deleterious effects of TNF in mammals, e.g. for treating conditions where there is an over prodn. of endogenous TNF, such as in cases of septic shock, cachexia; graft-versus-host reactions or autoimmune diseases like rheumatiod **arthritis**. It can also be used in cases of TNF intoxication caused by exogenous administration of excessive amts of TNF. Dwg.0/6

Abstract (US): 9623 US 5512544 A

A method for the treatment of an autoimmune disease or graft-versus-host reaction in a patient, comprising administering to the patient an effective amount of at least one protein selected from the group consisting of proteins having an amino acid sequence substantially corresponding to that of the binding site of the cell surface TNF receptors types I and II and that have the same ability to bind to TNF as natural or recombinant Tumour Necrosis Factor Binding Protein I (TBP-I) or Tumour Necrosis Factor Binding Protein II (TBP-II) is new.

Dwg.0/0

Abstract (EP): 9501 EP 308378 B

A Tumor Necrosis Factor (TNF) inhibitory Protein having the following features; (a) it inhibits the binding of TNF to its receptors and the cytotoxic effect of TNF; (b) when crude urine preparations thereof are chromatographed on an Ultrogel AcA 44 filtration column, the major peak of TNF inhibitory activity elutes slightly before the majority of the protein and shows an apparent molecular weight of about 40-80 KDa; and (c) when crude urine preparations thereof are analysed, the isoelectric point of the active protein is between pH6 and 8 or a salt, functional derivative or active fraction thereof, said active fraction having the ability to inhinit the binding of TNF to its respectors and the cytotoxic effect of TNF. Dwg.0/6

1/3,AB/9
DIALOG(R)File 351:DERWENT WPI

007667213 WPI Acc No: 88-301145/43
XRAM Acc No: C88-133427

animals when stimulated in vitro with lipopolysaccharide (LPS). The inhibitory effect of probucol was observed when IL 1 was assayed by the standard bioassay, the thymocyte proliferation assay, or a competitive IL 1 receptor binding assay. Probucol **treatment** had no effect on LPS-induced membrane IL 1 expression; secretion of **tumor** **necrosis** **factor** (**TNF**); Con A-induced splenic interleukin 2 (IL 2) and interleukin 3 (IL 3) release; and prostaglandin- or zymosan-induced secretion of prostacyclin, leukotriene C4, acid phosphatase, or superoxide anion. In contrast to the effect of oral administration, direct addition of probucol to macrophage cultures did not inhibit IL 1 release. Probucol administration did, however, inhibit the fall in serum zinc level induced by intravenous injection of LPS in zymosan-primed mice but had no effect on the LPS-induced increase in serum triglyceride levels, which indirectly confirms that probucol administration inhibits IL 1 but not **TNF** secretion. Paw granuloma induced in mice by heat-killed mycobacteria was inhibited by oral administration of probucol, an effect that may be attributable to inhibition of IL 1 secretion. Probucol neither reduced zymosan-induced liver granulomata in mice nor inhibited adjuvant-induced **arthritis** in rats. We suggest that inhibition of IL 1 secretion from macrophages by probucol contributes to its **therapeutic** effects in atherosclerosis and may also result in beneficial activity in some chronic inflammatory diseases.

6/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

07290674 90197674
Cytokines and cytokine inhibitors or **antagonists** in **rheumatoid** **arthritis**.
Arend WP; Dayer JM
Department of Medicine, University of Colorado Health Sciences Center, Denver 80262.
Arthritis Rheum (UNITED STATES) Mar 1990, 33 (3) p305-15, ISSN 0004-3591 Journal Code: 90M
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
This review has summarized some of the evidence suggesting that cytokines may play an important role in mediating pathophysiologic events in RA. However, these proteins are capable of mediating both stimulatory (agonist) and inhibitory (**antagonist**) effects in the rheumatoid synovium. GM-CSF, IL-1, **TNF** alpha, and PDGF are all produced in the rheumatoid synovium and may function to induce inflammation, enzyme release, fibroblast proliferation, and tissue destruction. Local release of IL-6 may alter the effects of IL-1 and **TNF** alpha, as well as induce Ig production and hepatic synthesis of acute-phase proteins. However, specific inhibitors of IL-1 and **TNF** alpha exist, which, if also released into the synovium, may antagonize the proinflammatory effects of these cytokines. In addition, IL-1 may have antiinflammatory effects, such as the induction of the synthesis of collagen and enzyme inhibitors by chondrocytes and synovial fibroblasts. Stimulation of these latter cells by TGF beta also may result in decreased matrix degradation and increased formation of scar tissue. The developing scenario is one of cell-cell interactions that are influenced in positive and negative manners by the local release of various mediators. A further understanding of cytokines and cytokine inhibitors in the rheumatoid synovium may lead to the development of more specific and effective **therapeutic** agents.

6/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

07243775 90150775
Enhanced cytotoxicity in the rheumatoid joint.
LaCour EG; Grayson MH; Ware CF; Pope RM
Northwestern University School of Medicine, Department of Medicine, Chicago, Illinois.
Clin Immunol Immunopathol (UNITED STATES) Mar 1990, 54 (3) p431-41, ISSN 0090-1229 Journal Code: DEA
Contract/Grant No.: PO60 AM30692, AM, NIADDK; CA35638, CA, NCI

individuals. The finding of a repeated release of **TNF**-BP-I into the circulation with intermittent injections of heparin indicates that **TNF** -BP-I is present both in a storage pool and in a circulating pool. The mechanism for the heparin-mediated release of **TNF** -BP-I was not explained; **TNF**-BP did not show affinity for heparin. On the other hand, **TNF** was found to have affinity for heparin and it could also be dissociated from heparin by **TNF**-BP-I. It is suggested that heparin-like molecules of the extracellular matrix can retain **TNF** in physical proximity with target cells and restrict the actions of **TNF** and protect against systemic harmful manifestations.

3/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

07944636 92082636
Elevated levels of **soluble** interleukin 2 **receptor** and **tumor** **necrosis** **factor** in nasopharyngeal carcinoma.
Hsu MM; Ko JY; Chang YL
Department of Otolaryngology, College of Medicine, National Taiwan University, Taipei.
Arch Otolaryngol Head Neck Surg (UNITED STATES) Nov 1991, 117 (11) p1257-9, ISSN 0886-4470 Journal Code: ALQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Depressed cell-mediated immunity as a measure of the mitogenic response of mononuclear cells in patients with nasopharyngeal carcinoma is well documented, but the mechanism is still unclear. The enzyme-linked immunosorbent assay was used to measure **soluble** interleukin 2 **receptor** and **tumor** **necrosis** **factor** levels in 295 patients with nasopharyngeal carcinoma and 97 age-matched control subjects. **Soluble** interleukin 2 **receptor** levels in patients with nasopharyngeal carcinoma were elevated and correlated with clinical staging. Higher **soluble** interleukin 2 **receptor** levels were found in patients with bone metastasis but not in patients with intracranial involvement. The levels of **tumor** **necrosis** **factor** in nasopharyngeal carcinoma were higher than in control subjects but did not correlate with clinical staging. These data suggest that **soluble** interleukin 2 **receptor** levels might be more useful than **soluble** **tumor** **necrosis** **factor** levels that indicate tumor bulk. **Soluble** interleukin 2 **receptor** serves as a blocking factor that competes with interleukin 2 function, resulting in a decreased mitogenic response in patients with nasopharyngeal carcinoma. The usefulness of the levels of **soluble** interleukin 2 **receptor** to monitor the efficacy of treatment in patients with nasopharyngeal carcinoma with bone metastasis requires further study.

3/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

07940859 92078859
A **tumor** **necrosis** **factor** (**TNF**) **receptor**-IgG heavy chain chimeric protein as a bivalent antagonist of **TNF** activity.
Peppel K; Crawford D; Beutler B
Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, Texas 75235.
J Exp Med (UNITED STATES) Dec 1 1991, 174 (6) p1483-9, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: PO1-DK42582-01, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using a multistep polymerase chain reaction method, we have produced a construct in which a cDNA sequence encoding the extracellular domain of the human 55-kD **tumor** **necrosis** **factor** (**TNF**) **receptor** is attached to a sequence encoding the Fc portion and hinge region of a mouse IgG1 heavy chain through an oligomer encoding a thrombin-sensitive peptide linker. This construct was placed downstream from a cytomegalovirus promoter sequence, and expressed in Chinese hamster ovary cells. A secreted protein, capable of binding **TNF** and inactivating it, was produced by

the transfected cells. Molecular characterization revealed that this **soluble** version of the **TNF** **receptor** was dimeric. Moreover, the protein could be quantitatively cleaved by treatment with thrombin. However, the monovalent extracellular domain prepared in this way has a greatly reduced **TNF** inhibitory activity compared with that of the bivalent inhibitor. Perhaps because of its high affinity for **TNF**, the chimeric protein is far more effective as a **TNF** inhibitor than are neutralizing monoclonal antibodies. This molecule may prove very useful as a reagent for the antagonism and assay of **TNF** and lymphotoxin from diverse species in health and disease, and as a means of deciphering the exact mechanism through which **TNF** interacts with the 55-kD **receptor**

3/3;AB/7
DIALOG(R)File 155:MEDLINE(R)
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07935320 92073320
Protection against endotoxic shock by a **tumor** **necrosis** **factor** **receptor** immunoadhesin.
Ashkenazi A; Marsters SA; Capon DJ; Chamow SM; Figari IS; Pennica D; Goeddel DV; Palladino MA; Smith DH
Department of Immunobiology, Genentech, Inc., South San Francisco, CA 94080.
Proc Natl Acad Sci U S A (UNITED STATES) Dec 1 1991, 88 (23) p10535-9, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factors** (**TNF**) alpha and beta are structurally related cytokines that mediate a wide range of immunological, inflammatory, and cytotoxic effects. During bacterial infection of the bloodstream (sepsis), **TNF** -alpha induction by bacterial endotoxin is thought to be a major factor contributing to the cardiovascular collapse and critical organ failure that can develop. Despite antibiotic therapy, these consequences of sepsis continue to have a high mortality rate in humans. Here we describe a potent **TNF** antagonist, a **TNF** **receptor** (**TNFR**) immunoadhesin, constructed by gene fusion of the extracellular portion of human type 1 **TNFR** with the constant domains of human IgG heavy chain (**TNFR**-IgG). When expressed in transfected human cells, **TNFR**-IgG is secreted as a disulfide-bonded homodimer. Purified **TNFR**-IgG binds to both **TNF**-alpha and **TNF**-beta and exhibits 6- to 8-fold higher affinity for **TNF**-alpha than cell surface or **soluble** **TNF** **receptors**. In vitro, **TNFR**-IgG blocks completely the cytolytic effect of **TNF**-alpha or **TNF** -beta on actinomycin D-treated cells and is markedly more efficient than **soluble** **TNFR** (24-fold) or monoclonal anti-**TNF** -alpha antibodies (4-fold) in inhibiting **TNF**-alpha. In vitro, **TNFR**-IgG prevents endotoxin-induced lethality in mice when given 0.5 hr prior to endotoxin and provides significant protection when given up to 1 hr after endotoxin challenge. These results confirm the importance of **TNF**-alpha in the pathogenesis of septic shock and suggest a clinical potential for **TNFR**-IgG as a preventive and therapeutic treatment in sepsis.

3/3,AB/8
DIALOG(R)File 155:MEDLINE(R)
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07906330 92044330
Tumor **necrosis** **factor** induces rapid production of 1'2'diacylglycerol by a phosphatidylcholine-specific phospholipase C.
Schutze S; Berkovic D; Tomsing O; Unger C; Kronke M
Institut fur Medizinische Mikrobiologie und Hygiene, Technische Universitat Munchen, Germany.
J Exp Med (UNITED STATES) Nov 1 1991, 174 (5) p975-88, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factor** (**TNF**) is a proinflammatory polypeptide that is able to induce a great diversity of cellular responses via modulating the expression of a number of different genes. One major

07997760 92135760
Cooperation between **tumor** **necrosis** **factor** (**TNF**) and platelet-activating factor (PAF) in the inflammatory response.
Maestre C; Zarco P; Gomez-Guerrero C; Gonzalez E; Herrero-Beaumont G; Braquet M; Egido J
Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Spain.
J Lipid Mediat (NETHERLANDS) **1990**, 2 Suppl pS151-9, ISSN 0921-8319 Journal Code: A6K
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this paper we have examined the cooperation between TNF and PAF in the generation of superoxide anion (O2-) in vitro by polymorphonuclear cells (PMNs), as well as their ability to induce joint inflammation when injected into the knee of healthy rabbits. TNF and PAF directly stimulated the generation of a small amount of O2- by PMNs. TNF pretreatment of PMNs induced a certain synergy in the O2- production, when these cells were later stimulated with PAF. When PAF receptor antagonists were added, the O2- release was inhibited. The injection of either TNF or PAF into the knee joint of normal rabbits induced a dose-dependent accumulation of leukocytes in the synovial cavity 24 h after administration. When TNF was administered 1 h before PAF, a synergistic response in the accumulation of leukocytes in the joint fluid was noted. The administration of BN 52726 by the intraperitoneal route markedly inhibited the cell accumulation induced by TNF and PAF. Histological signs of inflammation were noted in the synovial lining of joints injected with TNF and PAF. These results suggest that TNF can amplify the inflammatory response induced by PAF. PAF antagonists can inhibit this effect and thus may be of therapeutic value in different pathological situations.

1/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

07959520 92097520
Transgenic mice expressing human **tumour** **necrosis** **factor**: a predictive genetic model of **arthritis**.
Keffer J; Probert L; Cazlaris H; Georgopoulos S; Kaslaris E; Kioussis D; Kollias G
Laboratory of Molecular Genetics, Hellenic Pasteur Institute, Athens, Greece.
EMBO J (ENGLAND) Dec **1991**, 10 (13) p4025-31, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have generated transgenic mouse lines carrying and expressing wild-type and 3'-modified human tumour necrosis factor (hTNF-alpha, cachectin) transgenes. We show that correct, endotoxin-responsive and macrophage-specific hTNF gene expression can be established in transgenic mice and we present evidence that the 3'-region of the hTNF gene may be involved in macrophage-specific transcription. Transgenic mice carrying 3'-modified hTNF transgenes shows deregulated patterns of expression and interestingly develop chronic inflammatory polyarthritis. Treatment of these arthritic mice with a monoclonal antibody against human TNF completely prevents development of this disease. Our results indicate a direct involvement of TNF in the pathogenesis of **arthritis**. Transgenic mice which predictably develop **arthritis** represent a novel genetic model by which the pathogenesis and treatment of this disease in humans may be further investigated.

1/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

07891123 92029123
Localization of **tumor** **necrosis** **factor** alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid **arthritis**.
Chu CQ; Field M; Feldmann M; Maini RN

independently H or 1-2C alkyl; R2 and R8 may for a double bond and the B ring may then form a pyridine, pyrimidine, oxazole or thiazole ring. Specifically claimed compounds include 2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro -(5H)-pyrrolo-(1,2-a)imidazole. Administration is parenteral, oral, topical or by inhalation.

USE/ADVANTAGE - For inhibition of TNF production by monocytes and/or macrophages (claimed). Conditions in which TNF is implicated' include rheumatoid **arthritis** and other arthritic conditions, septic shock, fever and myalgia due to infection, cachexia secondary to malignancy or immune edficiency, keloid formation, Crohn's disease etc. @(111pp Dwg.No.0/4)@

Abstract (US): 9421 US 5317019 A

Inhibition of the prodn. of interleukin-1 (IL-1) and tumour necrosis factor (TNF) by monocytes and/or macrophages comprises administration of a pyridyl-imidazoloazole or analogous deriv. of formula (I) or its non-toxic salt. In (I), W is opt. Me- or Et-substd. CH2CH2, CH=CH or N=CH, or O or SOm, where m is 0-2; n is 0-2; R0 (or R1) opt. 2-(1-4C alkyl)-substd. 4-pyridyl, and R1 (or R0) is opt. substd. Ph; and R2-R5 are each H, Me or Et, R2 and R4 together denote an extra C to C bond in a condensed pyridine or pyrimidine ring.

USE/ADVANTAGE - Cpds. (I) are therapeutics for inflammable conditions arising from the prodn. of excess Il-1 and/or TNF, e.g. rheumatoid **arthritis** or spondylitis, osteoarthritis, gouty **arthritis**, etc.; shock; sepsis; cachexia associated with AIDS, malignancy or infection; adult respiratory syndrome, Chrohn's disease; etc. Cpds. (I) control the adverse effects of excess IL-1 and/or TNF. Dwg.0/4

1/3,AB/6
DIALOG(R)File 351:DERWENT WPI
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008027228 WPI Acc No: 89-292340/40
XRAM Acc No: C89-129548

Compsn. contg. anti-**tumour** **necrosis** **factor** antibody - and anti-lymphocyte antibody, useful for treating shock related conditions

Patent Assignee: (CLLT) CELLTECH LTD
Author (Inventor): BUURMAN W
Patent Family:

CC Number	Kind	Date	Week	
WO 8908460	A	890921	8940	(Basic)
EP 403558	A	901227	9101	
GB 2233559	A	910116	9103	
JP 3503890	W	910829	9141	
GB 2233559	B	920304	9210	
US 5183657	A	930202	9308	
EP 403558	B1	950329	9517	
DE 68921979	E	950504	9523	

Priority Data (CC No Date): GB 885792 (880311); GB 9019703 (900904)
Applications (CC,No,Date): DE 621979 (890313); EP 89904126 (890313); WO 89GB254 (890313); WO 89GB254 (890313); EP 89904126 (890313); JP 89503670 (890313); WO 89GB254 (890313); US 585065 (901022); US 881317 (920507); EP 89904126 (890313); WO 89GB254 (890313)

Abstract (Basic): WO 8908460 A

Compsn. comprises an antibody against human alpha-tumour necrosis factor (TNFalpha) and an antilymphocyte with carriers, excipients or diluents. Also claimed is an antibody against human alpha-tumour necrosis factor for use in the prevention or treatment of shock-related conditions arising from antilymphocyte antibody therapy. USE - Diseases which may be treated include autoimmune diseases, such as thyroiditis or rheumatoid **arthritis**, and rejection episodes following an organ or tissue transplant. Dwg.0/0

Abstract (US): 9308 US 5183657 A

Pharmaceutical compsn. comprises an antibody to human tumour necrosis factor-alpha and an anti-lymphocyte antibody. The latter is pref. MAb Orthoclone OKT3.

USE/ADVANTAGE - For immunoregulation in treating and preventing shock conditions arising from antilymphocyte antibody therapy. Dwg.0/0

Abstract (GB): 9210 GB 2233559

Set Items Description
S1 888 SOLUBLE? AND RECEPTOR? AND (TNF? OR (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?)
S2 136 S1 NOT PY>=1992
S3 66 S2 AND (TNF?/TI OR (TUMOUR OR TUMOR)(W)NECROSIS(W)FACTOR?/TI)
?□s3/3,ab/all

3/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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08034307 92172307
Inflammatory cytokines: interleukin-1 and **tumor** **necrosis** **factor** as effector molecules in autoimmune diseases.
Dinarello CA
Tufts University, Boston, Massachusetts.
Curr Opin Immunol (ENGLAND) Dec 1991, 3 (6) p941-8, ISSN 0952-7915
Journal Code: AH1
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The nature of the events that precipitate autoimmune diseases varies. Interleukin-1 and **tumor** **necrosis** **factor** do not precipitate autoimmune diseases but rather act as effector molecules. They induce eicosanoid and nitric oxide synthesis, stimulate collagenases and collagen synthesis, and trigger the genes for other cytokines, namely interleukin-2, interleukin-6 and interleukin-8. The ability to block interleukin-1 with the **receptor** antagonist, and **tumor** **necrosis** **factor** with **soluble** **receptors** , has given investigators specific tools to test the role of these two cytokines in the pathological processes of autoimmune disease.

3/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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08004967 92142967
Soluble and cell surface **receptors** for **tumor** **necrosis** **factor**.
Wallach D; Engelmann H; Nophar Y; Aderka D; Kemper O; Hornik V; Holtmann H; Brakebusch C
Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.
Agents Actions Suppl (SWITZERLAND) 1991, 35 p51-7, ISSN 0379-0363
Journal Code: 2YH
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW LITERATURE
Tumor **necrosis** **factor** (**TNF**) initiates its multiple effects on cell function by binding at a high affinity to specific cell surface **receptors**. Two different molecular species of these **receptors** , which are expressed differentially in different cells, have been identified. The cDNAs of both **receptors** have recently been cloned. Antibodies to one of these **receptor** species (the p55, type I **receptor**) can trigger a variety of **TNF** like effects by cross-linking of the **receptor** molecules. Thus, it is not **TNF** itself but its **receptors** that provide the signal for the response to this cytokine. The intracellular domains of the two **receptors** differ in structure, suggesting that they mediate different activities. Their extracellular domains, however, are structurally related. Both contain cysteine-rich repeats which are homologous to repeated structures found in the extracellular domains of the nerve growth factor **receptor** and the CDw40 protein. Truncated **soluble** forms of the two **receptors**, corresponding to these cysteine-rich repeated structures, have been detected in human urine and were later found to be present also in the serum. The serum levels of those **soluble** **TNF** **receptors** increase dramatically in certain pathological situations. Release of the **soluble** **receptors** from the cells seems to occur by proteolytic cleavage of the cell surface forms and appears to be a way of down-regulating the cell response to **TNF**. Because of their ability to bind **TNF**, the **soluble** **receptors** exert an inhibitory effect on **TNF** function, and may thus act as physiological attenuators of its activity.

3/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

07953731 92091731
Tumor **necrosis** **factor** (**TNF**) **receptor** expression in T lymphocytes. Differential regulation of the type I **TNF** **receptor** during activation of resting and effector T cells.
Ware CF; Crowe PD; Vanarsdale TL; Andrews JL; Grayson MH; Jerzy R; Smith CA; Goodwin RG
Division of Biomedical Sciences, University of California, Riverside 92521.
J Immunol (UNITED STATES) Dec 15 1991, 147 (12) p4229-38, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The expression of **TNF**-alpha **receptors** (**TNFR**) was examined on a CD4+ T cell hybridoma, transformed T cell lines, CTL clones, and activated T cells from peripheral blood to determine the basis of the immunomodulatory activity of **TNF** on T cell function. Analyses by ligand cross-linking and competitive binding assays with mAb to the 80-kDa **receptor** (**TNFR**-I), demonstrated that the **TNFR** -I was the predominant **receptor** expressed on activated CD4+ and CD8+ T cell subsets. However, on T cell leukemic lines, a second, non-**TNFR**-I binding site was identified, most likely the 55-kDa form (**TNFR**-II). Additional subsets of T cells were readily distinguished by their expression of **TNFR**-I and related members of the **TNFR** gene family (CD40 and CD27). Expression of the **TNFR**-I was dependent upon the state of T cell activation. Signaling through the TCR for Ag or IL-2R was sufficient to induce **TNFR** mRNA and protein expression in resting T cells. Multiple sizes of **TNFR**-I transcripts were detected during T cell activation; however, biosynthetic studies showed these multiple species encode a single protein of 80 kDa. These results, combined with the known ability of **TNF** to induce IL-2R expression, indicate that **TNF** and IL-2 form a reciprocating **receptor** amplification circuit. In contrast, differentiated effector T cells triggered through the TCR or protein kinase C initiated a rapid down-regulation (transmodulation) of the **TNFR**-I that preceded **TNF** or lymphotoxin secretion. The mechanism of transmodulation involved proteolytic processing of the mature 80-kDa **receptor** releasing a **soluble** 40-kDa fragment. This indicates that a **TNF** autocrine loop is not likely to form during the response of an effector T cell. Collectively, these results suggest that transcriptional and post-translational modification of the **TNFR**-I are important control points regulating the expression of this **receptor** during T cell activation.

3/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

07953515 92091515
On the binding of **tumor** **necrosis** **factor** (**TNF**) to heparin and the release in vivo of the **TNF**-binding protein I by heparin.
Lantz M; Thysell H; Nilsson E; Olsson I
Department of Medicine, University Hospital, Lund, Sweden.
J Clin Invest (UNITED STATES) Dec 1991, 88 (6) p2026-31, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factor** (**TNF**), a protein released by activated macrophages, is a central mediator of the host response to infection and inflammation. The **TNF**-binding protein I (**TNF**-BP-I) is a **soluble** fragment of the p60 transmembrane **TNF** **receptor** and an antagonist to **TNF**. The level of serum **TNF**-BP-I was found to be increased in patients with renal insufficiency as a result of a decrease in the glomerular filtration rate. During hemodialysis of patients with renal failure there was a rapid but transient increase in serum **TNF**-BP-I. This increase was found to be caused by heparin given before dialysis and a similar dose-dependent response to heparin was observed also in healthy

pathway by which **TNF** **receptors** communicate signals from the membrane to the cell nucleus involves protein kinase C (PKC). In the present study, we have addressed the molecular mechanism of **TNF**-induced PKC activation. To this, membrane lipids of the human histiocytic cell line U937 were labeled by incubation with various radioactive precursors, and **TNF**-induced changes in phospholipid, neutral lipid, and water-**soluble** metabolites were analyzed by thin layer chromatography. **TNF** treatment of U937 cells resulted in a rapid and transient increase of 1'2'diacylglycerol (DAG), a well-known activator of PKC. The increase in DAG was detectable as early as 15 s after **TNF** treatment and peaked at 60 s. DAG increments were most pronounced (approximately 360% of basal levels) when cells were preincubated with [14C]lysophosphatidylcholine, which was predominantly incorporated into the phosphatidylcholine (PC) pool of the plasma-membranes. Further extensive examination of changes in metabolically labeled phospholipids indicated that **TNF** -stimulated hydrolysis of PC is accompanied by the generation of phosphorylcholine and DAG. These results suggest the operation of a PC-specific phospholipase C. Since no changes in phosphatidic acid (PA) and choline were observed and the production of DAG by **TNF** could not be blocked by either propranolol or ethanol, a combined activation of phospholipase D and PA-phosphohydrolase in DAG production appears unlikely. **TNF**-stimulated DAG production as well as PKC activation could be blocked by the phospholipase inhibitor p-bromophenacylbromide (BPB). Since BPB did not inactivate PKC directly, these findings underscore that **TNF** activates PKC via formation of DAG. **TNF** stimulation of DAG production could be inhibited by preincubation of cells with a monoclonal anti-**TNF** **receptor** (p55-60) antibody, indicating that activation of a PC-specific phospholipase C is a **TNF** **receptor**-mediated event.

3/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

07899839 92037839
Recombinant **soluble** **tumor** **necrosis** **factor** **receptor** proteins protect mice from lipopolysaccharide-induced lethality.
Lesslauer W; Tabuchi H; Gentz R; Brockhaus M; Schlaeger EJ; Grau G; Piguet PF; Pointaire P; Vassalli P; Loetscher H
F. Hoffmann-La Roche Ltd., Basel, Switzerland.
Eur J Immunol (GERMANY) Nov 1991, 21 (11) p2883-6, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The in vivo efficacy of human recombinant **soluble** **tumor** **necrosis** **factor** (**TNF**) **receptor** protein to prevent and to treat lipopolysaccharide (LPS)-induced lethal toxicity in D-galactosamine-treated mice was investigated. Chimeric proteins of the **receptor** extracellular domains fused to the hinge region of human IgG3 were expressed in myeloma cells (rsTNFR-h gamma 3). The fusion proteins had a disulfide-bonded dimeric structure. Upon intravenous injection, their serum concentration decreased relatively slowly after an initial phase of rapid elimination. D-galactosamine-sensitized mice were fully protected from the toxic effects of LPS, if the animal were pretreated with rsTNFR-h gamma 3 at 20 micrograms/animal. Partial protection was seen at significantly lower doses and when rsTNFR-h gamma 3 was given up to 3 h after LPS.

3/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

07875198 92013198
A monoclonal antibody-based enzyme immunoassay for quantitation of human **tumor** **necrosis** **factor** binding protein I, a **soluble** fragment of the 60 kDa **TNF** **receptor**, in biological fluids.
Adolf GR; Apfler I
Ernst Boehringer-Institut fur Arzneimittelforschung, Bender & Co. Ges mbH, Department of Cell Biology, Vienna, Austria.
J Immunol Methods (NETHERLANDS) Sep 20 1991, 143 (1) p127-36, ISSN 0022-1759 Journal Code: IFE

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Three hybridoma cell lines secreting monoclonal IgG antibodies specific for human **tumor** **necrosis** **factor**-binding protein I (**TNF**-BP I), the extracellular domain of the 60 kDa **TNF** **receptor**, were developed by fusion of spleen cells from mice immunized with **TNF**-BP I purified from urine. The antibodies recognize three different epitopes on **TNF** -BP I. Two of the antibodies were used to develop a two-site ('sandwich') enzyme immunoassay with horseradish peroxidase as the marker enzyme. The assay was able to measure **TNF**-BP I in serum, urine and cell culture supernatants with a sensitivity of about 200 ng/l and a precision better than 10%. **TNF** -BP I was detected in the serum of healthy individuals at a mean concentration of 2.1 +/- 1.0 micrograms/l (mean +/- standard deviation; range, 0.52-5.4 microgram/l, n = 42); no significant difference was seen in patients with chronic polyarthritis (2.3 +/- 0.79 micrograms/l; n = 15). Serum **TNF**-BP I was significantly elevated in patients with burns (6.5 +/- 1.7 micrograms/l; n = 10) and markedly increased in patients with renal failure (49 +/- 17 micrograms/l; n = 6). **TNF** -BP I was also detectable in urine from normal individuals (2.2 +/- 1.2 micrograms/l; range 0.78-4.3 micrograms/l; n = 16). Culture supernatants of several human tumor cell lines also contained **TNF**-BP I. The assay will be a useful tool to detect activation of the **TNF** **receptor** by the physiological ligands, **TNF**-alpha and **TNF**-beta, as well as transmodulation by other mediators in various pathological conditions.

3/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

07873651 92011651
Human neutrophil elastase releases a ligand-binding fragment from the 75-kDa **tumor** **necrosis** **factor** (**TNF**) **receptor**. Comparison with the proteolytic activity responsible for shedding of **TNF** **receptors** from stimulated neutrophils.
Porteu F; Brockhaus M; Wallach D; Engelmann H; Nathan CF
Beatrice and Samuel A. Seaver Laboratory, Department of Medicine, Cornell University Medical College, New York, New York 10021.
J Biol Chem (UNITED STATES) Oct 5 1991, 266 (28) p18846-53, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA45218, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To localize the protease(s) involved in shedding of **tumor** **necrosis** **factor** **receptors** (**TNF** -R) from activated neutrophils (PMN) (Porteu, F., and C. Nathan (1990) J. Exp. Med. 172, 599-607), we tested subcellular fractions from PMN for their ability to cause loss of **TNF** -R from intact cells. Exposure of PMN to sonicated azurophil granules at 37 degrees C resulted in inhibition of 125I-**TNF** binding; 50% inhibition ensued when PMN were treated for approximately 1 min with azurophil granules equivalent to 2-3 PMN per indicator cell. The **TNF** -R-degrading activity in azurophil granules were identified as elastase by its sensitivity to diisopropyl fluorophosphate (DFP), alpha 1-antitrypsin and N-methoxysuccinyl-Ala-Ala-Pro-Val chloromethyl ketone (MSAAPV-CK), and by the ability of purified elastase to reproduce the effect of azurophil granules. Elastase preferentially acted on the 75-kDa **TNF**-R, reducing by 85-96% the binding of 125I-**TNF** to mononuclear cells expressing predominantly this **receptor**, while having no effect on endothelial cells expressing almost exclusively the 55-kDa **TNF**-R. Elastase-treated PMN released a 32-kDa **soluble** fragment of p75 **TNF** -R that bound **TNF** and reacted with anti-**TNF** -R monoclonal antibodies. In contrast, fMet-Leu-Phe-activated PMN shed a 42-kDa fragment from p75 **TNF** -R, along with similar amounts of a 28-kDa fragment from p55 **TNF**-R. Shedding of both **TNF**-Rs by intact activated PMN was more extensive than shedding caused by elastase and was completely resistant to DFP and MSAAPV-CK. Thus, the **TNF**-R-releasing activity of azurophil granules is distinct from that operative in intact stimulated PMN and could provide an additional mechanism for the control of cellular responses to **TNF** at sites of inflammation.

3/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

07873571 92011571
Recombinant 55-kDa **tumor** **necrosis** **factor** (**TNF**) **receptor**. Stoichiometry of binding to **TNF** alpha and **TNF** beta and inhibition of **TNF** activity.
Loetscher H; Gentz R; Zulauf M; Lustig A; Tabuchi H; Schlaeger EJ; Brockhaus M; Gallati H; Manneberg M; Lesslauer W
Pharma Research New Technologies, F. Hoffmann-LaRoche Ltd., Basel, Switzerland.
J Biol Chem (UNITED STATES) Sep 25 1991, 266 (27) p18324-9, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The extracellular domain of the 55-kDa **TNF** **receptor** (rsTNFR beta) has been expressed as a secreted protein in baculovirus-infected insect cells and Chinese hamster ovary (CHO)/dhfr- cells. A chimeric fusion protein (rsTNFR beta-h gamma 3) constructed by inserting the extracellular part of the **receptor** in front of the hinge region of the human IgG C gamma 3 chain has been expressed in mouse myeloma cells. The recombinant **receptor** proteins were purified from transfected cell culture supernatants by **TNF** alpha- or protein G affinity chromatography and gel filtration. In a solid phase binding assay rsTNFR beta was found to bind **TNF** alpha with high affinity comparable with the membrane-bound full-length **receptor**. The affinity for **TNF** beta was slightly impaired. However, the bivalent rsTNFR beta-h gamma 3 fusion protein bound both ligands with a significantly higher affinity than monovalent rsTNFR beta reflecting most likely an increased avidity of the bivalent construct. A molecular mass of about 140 kDa for both rsTNFR beta.**TNF** alpha and rsTNFR beta.**TNF** beta complexes was determined in analytical ultracentrifugation studies strongly suggesting a stoichiometry of three rsTNFR beta molecules bound to one **TNF** alpha or **TNF** beta trimer. Sedimentation velocity and quasielastic light scattering measurements indicated an extended structure for rsTNFR beta and its **TNF** alpha and **TNF** beta complexes. Multiple **receptor** binding sites on **TNF** alpha trimers could also be demonstrated by a **TNF** alpha-induced agglutination of Latex beads coated with the rsTNFR beta-h gamma 3 fusion protein. Both rsTNFR beta and rsTNFR beta-h gamma 3 were found to inhibit binding of **TNF** alpha and **TNF** beta to native 55- and 75-kDa **TNF** **receptors** and to prevent **TNF** alpha and **TNF** beta bioactivity in a cellular cytotoxicity assay. Concentrations of rsTNFR beta-h gamma 3 equimolar to **TNF** alpha were sufficient to neutralize **TNF** activity almost completely, whereas a 10-100-fold excess of rsTNFR beta was needed for similar inhibitory effects. In view of their potent **TNF** antagonizing activity, recombinant **soluble** **TNF** **receptor** fragments might be useful as therapeutic agents in **TNF**-mediated disorders.

3/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

07867499 92005499
Increased serum levels of **soluble** **receptors** for **tumor** **necrosis** **factor** in cancer patients.
Aderka D; Englemann H; Hornik V; Skornick Y; Levo Y; Wallach D; Kushtai G
Department of Medicine, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel Aviv University, Israel.
Cancer Res (UNITED STATES) Oct 15 1991, 51 (20) p5602-7, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Soluble forms of the two molecular species of the cell surface **receptors** for **tumor** **necrosis** **factor** (**TNF**) have been detected in normal urine. Using enzyme-linked immunosorbent assays for these **soluble** **receptors**, we determined their levels in the sera of 40 healthy subjects and 59 patients with solid tumors. The mean +/- SD concentrations of both the **soluble** type I (p55) and type II (p75) **receptors** were significantly higher in the cancer patients than in the

healthy controls: 1.96 +/- 1.19 versus 0.79 +/- 0.19 ng/ml (P less than 0.001) and 6.43 +/- 4.8 versus 3.2 +/- 0.6 ng/ml (P less than 0.001), respectively. The incidence and the extent of the increase correlated with the staging of disease. Sera of the cancer patients had a marked inhibitory effect on the in vitro cytocidal activity of **TNF**. This inhibition was proportional to the content of **soluble** **TNF** **receptors** and could be fully abolished by the addition to the sera of specific antibodies against the **receptors** . Among the cancer patients, the incidence of increase in the concentrations of **soluble** **TNF** **receptors** (about 70%) greatly exceeded that of the serum carcinoembryonic antigen (about 26%), a commonly used cancer marker. The origin of the serum **soluble** **TNF** **receptors** in cancer patients and the physiological implications of their effect on **TNF** function remain to be elucidated.

3/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

07857863 91376863
Soluble CD8, IL-2 **receptor**, and **tumor** **necrosis** **factor** -alpha levels in steroid-resistant acute graft-versus-host disease. Relation with subsequent response to anti-IL-2 **receptor** monoclonal antibody treatment.
Tiberghien P; Racadot E; Lioure B; Delain M; Girard A; Wijdenes J; Plouvier E; Flesch M; Cahn JY; Herve P
Service d'Hematologie, CHU Besancon, France.
Transplantation (UNITED STATES) Sep 1991, 52 (3) p475-80, ISSN 0041-1337 Journal Code: WEJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serial determination of **soluble** CD8 (sCD8), **soluble** IL-2 **receptors** (sIL-2R), and **tumor** **necrosis** **factor**-alpha serum levels were performed in bone marrow transplant patients upon initiation, day 0 (D0) and at D10 of an anti-IL-2 **receptor** (alpha chain) monoclonal antibody (B-B10) in vivo treatment for steroid-resistant grade greater than or equal to 2 acute graft-versus-host disease (aGVHD). D0 and D10 sCD8 serum levels correlated strongly with response to B-B10 treatment (p = .003 and .001, respectively); 76% of the patients with D0 sCD8 levels less than 500 U/ml responded favorably to B-B10 treatment, versus only a 30% response if the sCD8 levels were greater than 500 U/ml (p = .02). Likewise, D0 **tumor** **necrosis** **factor** -alpha levels significantly correlated with subsequent response to B-B10 treatment (p = .03). D0 sIL-2R levels were not significantly different in B-B10-responsive and nonresponsive aGVHD patients. These results suggest that the serial determination of sCD8 and **TNF** serum levels could provide valuable predictive information as to steroid-resistant aGVHD responsiveness to anti-IL-2R treatment.

3/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

07853940 91372940
A role for gamma interferon, **tumor** **necrosis** **factors**, and **soluble** T-cell **receptors** in the depressed blastogenic response of spleen cells of Mycobacterium lepraemurium-infected mice.
Richard L; Forget A; Turcotte R
Applied Microbiology Research Center, Institut Armand-Frappier, Universite du Quebec, Laval, Canada.
Infect Immun (UNITED STATES) Oct 1991, 59 (10) p3387-92, ISSN 0019-9567 Journal Code: GO7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Spleen cells of Mycobacterium lepraemurium-infected mice were cultured on petri dishes coated with mycobacterial antigens, and antigen-reactive cells were isolated. Upon incubation in mitogen- or antigen-free culture medium, these cells released mediators capable of depressing the in vitro proliferative response of normal splenocytes to specific antigen and to concanavalin A and lipopolysaccharide. One of these mediators was identified with gamma interferon (IFN-gamma), mainly on the basis that treatment of supernatants with monoclonal anti-IFN-gamma antibodies

markedly reduced the suppressive activity contained therein. Detectable levels of **tumor** **necrosis** **factor** alpha (**TNF**-alpha) and **TNF** -beta were present in spleen cell culture supernatants of infected mice. Moreover, low doses of recombinant **TNF**-alpha and **TNF**-beta were found to potentiate the suppressive activity of exogenous IFN-gamma. **Soluble** T-cell **receptors** beta were also detected in the culture supernatants. The elimination of these molecules with monoclonal anti-T-cell **receptor** beta (F23.1) antibodies immobilized on a plastic surface partially reversed the depression of the response to mycobacterial antigen but did not affect the response to mitogens. These results revealed the complex nature of suppressor mediators that are produced by mycobacterial antigen-reactive cells and that regulate the in vitro proliferative response.

3/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

07851705 91370705
Infusion of **tumor** **necrosis** **factor** (**TNF**) causes an increase in circulating **TNF**-binding protein in humans.
Lantz M; Malik S; Slevin ML; Olsson I
Division of Hematology, Department of Medicine, Lund, Sweden.
Cytokine (UNITED STATES) Nov 1990, 2 (6) p402-6, ISSN 1043-4666 Journal Code: A52
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serum samples from cancer patients receiving intravenous infusions of recombinant **tumor** **necrosis** **factor** (rTNF) and recombinant interferon-gamma (rIFN-gamma) were analyzed for **TNF** and the **TNF** -binding protein (**TNF**-BP). **TNF**-BP is a **soluble** fragment of the transmembrane **TNF** **receptor** with antagonistic effects to **TNF** and is released by proteolytic cleavage of the **receptor**. During a 60-min infusion of rTNF, peak serum levels of rTNF were observed after 30 to 60 min and a transient increase of circulating **TNF**-BP was observed with peak levels between 30 and 120 min. Injection of IFN-gamma alone did not affect the levels of **TNF** and **TNF**-BP. Thus administration of rTNF leads to release into the circulation of **TNF**-BP, which may modulate both systemic and local effects of **TNF** and influence its therapeutic efficacy.

3/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

07837560 91356560
Cytolytic activities of activated macrophages versus paraformaldehyde-fixed macrophages; **soluble** versus membrane-associated **TNF**.
Fishman M
Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101-0318.
Cell Immunol (UNITED STATES) Oct 1 1991, 137 (1) p164-74, ISSN 0008-8749 Journal Code: CQ9
Contract/Grant No.: CA-18672, CA, NCI; P30CA-21765, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Membrane-associated **tumor** **necrosis** **factor** (**TNF**) and **soluble** **TNF** were compared as to their lytic activities, and as to the kinetics of their expression by macrophages activated with LPS and/or IFN-gamma in the presence or absence of cycloheximide. EL 4 tumor cells, resistant and sensitive to lysis by recombinant **TNF** or membrane-associated **TNF** (paraformaldehyde (PF)-fixed activated macrophages) were used as targets. In the presence of cycloheximide the **TNF**-resistant S-EL4 cells were lysed by both **TNFs** . PF-fixed macrophages was cytolytic after 1 hr activation but not after 3 or more hours of activation. Their activity was totally inhibited by anti-**TNF** antibodies and was a composite of transmembrane (integral) **TNF** and **soluble** **TNF** conjugated to macrophage membrane **TNF** **receptors** . Treatment of the macrophages with glycine pH 3.0 buffer dissociated the

conjugated **TNF** without affecting the integral membrane **TNF**. When macrophages were activated with LPS +/- IFN-gamma in the presence of cycloheximide or activated just with IFN-gamma their activity after fixation with paraformaldehyde was no longer detected. Nonfixed macrophages under these conditions still remained cytotoxic. Tumor cell susceptibility to membrane-associated **TNF** activity, in contrast to recombinant (**soluble**) **TNF**, was greatly reduced in the presence of nicotinamide, an inhibitor of ADP-ribosyltransferase, suggesting that the mechanisms of lysis by these **TNFs** may be different. The lytic activity of both **TNFs** was found to be **receptor**-dependent in that tumor cells, whose **TNF** binding sites were "down-regulated" by TPA, were rendered resistant to lysis by both membrane-associated and **soluble** **TNFs**.

3/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

07830608 91349608
Development of immunoassays for the detection of **soluble** **tumour** **necrosis** **factor** **receptors**.
Liabakk NB; Sundan A; Waage A; Brockhaus M; Loetcher H; Lesslauer W; Espevik T
UNIGEN, University of Trondheim, Norway.
J Immunol Methods (NETHERLANDS) Aug 9 1991, 141 (2) p237-43, ISSN 0022-1759 Journal Code: IFE
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Immunoassays were established for the detection of the 55 kDa and 75 kDa **tumour** **necrosis** **factor** **receptor** (**TNFR**) fragments present in urine. The immunoassays were based on pairs of monoclonal **TNFR** antibodies directed against different epitopes of the 55 kDa and 75 kDa **TNFRs**. The immunoassays were judged to be specific for unoccupied **TNFR** since the signals were inhibited by adding recombinant human or murine **TNF**-alpha, and to a lesser extent by rTNF-beta (LT). Other cytokines such as IL-1 beta, IL-2 or rIFN-gamma did not affect the signal. In a preliminary screening it was found that urines from febrile patients contained higher amounts of 55 kDa and 75 kDa **TNFR** fragments than did urine from non-febrile individuals. The immunoassays could be used to monitor the purification of the two types of **TNFR** from the same febrile urine. Furthermore, the sensitivity and the speed of the assay could be increased by the use of magnetic beads as a solid support in the assay.

3/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

07828006 91347006
Levels of **soluble** low affinity IL2 **receptors** (s-IL2 R) and **TNF** in the serum after BMT.
Alessandrino EP; Bernasconi P; Colombo A; Boni M; Bonfichi M; Caldera D; Bernasconi C
Centro Trapianti di Midollo Osseo, Divisione di Ematologia, Policlinico S. Matteo IRCCS, Pavia.
Bone Marrow Transplant (ENGLAND) 1991, 7 Suppl 2 p51, ISSN 0268-3369 Journal Code: BON
Languages: ENGLISH
Document type: JOURNAL ARTICLE

3/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

07814273 91333273
Evidence for different effects of **soluble** **TNF**-**receptors** on various **TNF** measurements in human biological fluids [letter; comment]
Engelberts I; Stephens S; Francot GJ; van der Linden CJ; Buurman WA
Lancet (ENGLAND) Aug 24 1991, 338 (8765) p515-6, ISSN 0140-6736 Journal Code: LOS

Comment on Lancet 1987 Nov 28;2(8570):1229-32
Languages: ENGLISH
Document type: COMMENT; LETTER

3/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

07780364 91299364
Serum levels of IL-2, IL-1 alpha, **TNF**-alpha, and **soluble** **receptor** of IL-2 in HIV-1-infected patients.
Scott-Algara D; Vuillier F; Marasescu M; de Saint Martin J; Dighiero G
Service d'Immunohematologie et d'Immunopathologie, Institut Pasteur, Paris, France.
AIDS Res Hum Retroviruses (UNITED STATES) Apr 1991, 7 (4) p381-6, ISSN 0889-2229 Journal Code: ART
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serum levels of the interleukins (IL-1 alpha, IL-2), **tumor** **necrosis** **factor**-alpha (**TNF**-alpha), and **soluble** **receptor** of IL-2 (sIL-2R) were studied by enzyme-linked immunosorbent assay (ELISA) in 12 normal healthy controls and 52 HIV-1 seropositive patients. Results indicated that: (1) sIL-2R levels were significantly increased in most HIV-1 seropositive patients. This increase appeared to be correlated with low CD4 cell counts and with the presence of detectable levels of p25 antigen. Furthermore, initially high levels of sIL-2R appeared to be correlated with progression of disease. (2) IL-2 levels were found to be increased in about 43% of asymptomatic carriers (ASY) and subjects with lymphoadenopathy-associated syndrome (LAS) compared with 12% in the case of AIDS-related complex (ARC) and AIDS patients. (3) There was a positive correlation between serum levels of **TNF**-alpha and IL-1 alpha in nearly all patients. Detectable levels of both cytokines were found in 34% of ASY and LAS patients and only rarely were detectable in ARC and AIDS patients. (4) Sixteen patients in whom progression of disease was observed were studied initially and at the moment they upstaged. No significant modification of serum levels of the three cytokines and sIL-2R studied could be evidenced. It was concluded that sIL-2R could be a useful marker of disease activity and progression, though a prospective study is necessary. For IL-2, IL-1 alpha, and **TNF**-alpha, this study indicated the presence of variable alterations in serum levels in HIV-1-infected patients.

3/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

07758215 91277215
Serum cytokine levels in chronic progressive multiple sclerosis: interleukin-2 levels parallel **tumor** **necrosis** **factor** -alpha levels.
Trotter JL; Collins KG; van der Veen RC
Washington University School of Medicine, Department of Neurology and Neurological Surgery (Neurology), St. Louis, MO 63110.
J Neuroimmunol (NETHERLANDS) Jul 1991, 33 (1) p29-36, ISSN 0165-5728 Journal Code: HSO
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serum levels of the cytokines interleukin-1 alpha (IL-I alpha), IL-1 beta, IL-2, IL-4, IL-6, **tumor** **necrosis** **factor**-alpha (**TNF** -alpha) and the **soluble** IL-2 **receptor** were measured in chronic progressive multiple sclerosis patients (CPMS) and normal, inflammatory, and noninflammatory disease controls. Serum IL-2 levels displayed the most consistent abnormalities in the group of tests for the CPMS group, and were the only cytokine levels to achieve significance in statistical group analyses. However, several patients with CPMS had normal serum IL-2 levels. An incidental finding was a statistical correlation between serum IL-2 and **TNF**-alpha levels among all groups tested. This finding was supported on analysis of serial serum samples from CPMS patients. These results suggest a linkage of IL-2 and **TNF**-alpha production, especially in pathological conditions.

3/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

07751991 91270991
TNF: antitumoral agent at the border lines of immunity and inflammation]
Le **TNF**: un agent antitumoral aux frontieres de l'immunite et de l'inflammation.
Branellec D; Chouaib S
UA 1156 CNRS, Institut Gustave-Roussy, Villejuif, France.
Pathol Biol (Paris) (FRANCE) Mar 1991, 39 (3) p230-9, ISSN 0369-8114 Journal Code: OSG .
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English Abstract
Tumor **Necrosis** **Factor**-alpha (**TNF**) is mainly produced by activated monocytes and exerts pleiotropic biological effects on a wide variety of both normal and transformed cells. Originally described for its capacity to induce hemorrhagic necrosis of transplantable tumors in vivo and cytolysis of some tumor cells in vitro, **TNF** has also been shown to play an essential role during the inflammatory response, exerting dual, both beneficial and deleterious, effects. **TNF**, via a local production appears to be a key cytokine involved in antiviral, antibacterial and antiparasitic host defense mechanisms. Contreversely, deregulation of the inflammatory and immune reactions can be associated with a systemic **TNF** production, leading to toxic secondary effects. Recent cloning of the **TNF** **receptors** has provided additional insights in the complex physiology of **TNF**. It is now clearly established that both type I and type II **TNF** **receptors** can be cleaved and released as **TNF** binding proteins. The **soluble** fragments of **TNF** **receptors** can inhibit **TNF** -mediated tumor cell lysis in vitro and might therefore serve as regulators of **TNF** action. The antitumor potency of **TNF** also reflects the pleiotropic aspect of **TNF**. **TNF**-induced tumor regression, observed in various preclinical studies, appears to result from at least three distinct biological effects: mainly hemorrhagic necrosis via **TNF** action on tumor endothelium, **TNF** immunomodulatory activity on immune effector cells, and presumably a direct **TNF**-mediated cytotoxic effect against tumor cells. From the clinical trials performed with distinct recombinant materials a consensus has emerged about the disappopinting anticancer efficacy of **TNF** used in systemic administration. Further studies, aimed at better understanding the complex action of **TNF**, are required to possibly enhance its therapeutic index and subsequently to assess whether **TNF** still remains a promising therapeutic agent.

3/3,AB/24
DIALOG(R)File 155:MEDLINE(R)

07726157 91245157
The proinflammatory cytokines interleukin-1 and **tumor** **necrosis** **factor** and treatment of the septic shock syndrome.
Dinarello CA
Department of Medicine, Tufts University, Boston, Massachusetts.
J Infect Dis (UNITED STATES) Jun 1991, 163 (6) p1177-84, ISSN 0022-1899 Journal Code: IH3
Contract/Grant No.: AL-15614
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Treating the septic shock syndrome with antibodies that block only endotoxin has its limitations. Other targets for treating septic shock include neutralizing antibodies to the complement fragment C5a, platelet-activating factor antagonists, and blockade of endothelial cell leukocyte adhesion molecules. Specific blockade of the proinflammatory cytokines interleukin-1 (IL-1) or **tumor** **necrosis** **factor** (**TNF**) reduces the morbidity and mortality associated with septic shock. Moreover, blocking IL-1 and **TNF** likely has uses in treating diseases other than septic shock. Use of neutralizing antibodies to **TNF** or to

IL-1 **receptors** have reduced the consequences of infection and inflammation, including lethal outcomes in animal models. The IL-1 **receptor** antagonist, a natural-occurring cytokine, blocks shock and death due to Escherichia coli and ameliorates a variety of inflammatory diseases. **Soluble** **TNF** and IL-1 surface **receptors**, which bind their respective cytokines, also ameliorate disease processes. Current clinical trials are evaluating the safety and efficacy of these anticytokine therapies either alone or together.

3/3,AB/25
DIALOG(R)File 155:MEDLINE(R)

07725343 91244343
Human immunoglobulin preparation for intravenous use induces elevation of cellular cyclic adenosine 3':5'-monophosphate levels, resulting in suppression of **tumour** **necrosis** **factor** alpha and interleukin-1 production.
Shimozato T; Iwata M; Kawada H; Tamura N
Biological Research Laboratories, Sankyo Co. Ltd., Tokyo, Japan.
Immunology (ENGLAND) Apr 1991, 72 (4) p497-501, ISSN 0019-2805
Journal Code: GH7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We previously showed that human immunoglobulin preparation for intravenous use (IGIV) suppresses the in vitro production of **tumour** **necrosis** **factor**-alpha (**TNF**-alpha) and interleukin-1 (IL-1) by rabbit peritoneal exudate cells (PEC) stimulated with lipopolysaccharide (LPS). In this study we investigated the mechanism of the suppression. IGIV treated at pH4 (pH4-G) was used as IGIV. Fc fragments of pH4-G, as well as untreated pH4-G, suppressed **TNF**-alpha and IL-1 production by rabbit PEC stimulated with LPS. The interaction of pH4-G with PEC also resulted in generation of cyclic adenosine 3':5'-monophosphate (cAMP), known to be an intracellular second messenger. N6, 2'-0-dibutyryl cAMP (BtcAMP), a lipid-**soluble** derivative of cAMP, and cholera toxin (CT), an adenylate cyclase activating agent, also suppressed the production of **TNF**-alpha and IL-1. Further N-[2-(methylamino) ethyl]-5-isoquinolinesulphonamide dihydrochloride (H-8), an inhibitor of cAMP-dependent protein kinases, abrogated the suppression by pH4-G of the productions. These results indicate that the binding of IGIV to PEC via Fc gamma **receptors** (Fc gamma R) induces the elevation of intracellular cAMP levels, resulting in the suppression of LPS-induced **TNF**-alpha and IL-1 productions.

3/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

07692360 91211360
CD18 adhesion **receptors**, **tumor** **necrosis** **factor**, and neutropenia during septic lung injury.
Walsh CJ; Leeper-Woodford SK; Carey PD; Cook DJ; Bechard DE; Fowler AA; Sugerman HJ
Department of Surgery, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0519.
J Surg Res (UNITED STATES) Apr 1991, 50 (4) p323-9, ISSN 0022-4804
Journal Code: K7B
Contract/Grant No.: HL 35534, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Sequestration of neutrophils (PMNs) in the pulmonary microvasculature and associated neutropenia are characteristic features of experimental models of septic lung injury. The etiology of altered PMN kinetics during septic lung injury is uncertain, but may be partially due to increased adhesiveness of activated PMNs to pulmonary endothelium. This study examines the relationship between the expression of PMN CD18 adhesion **receptors**, the evolving neutropenia, and plasma **tumor** **necrosis** **factor** (**TNF**) activity in a porcine model of septic lung injury. Acute lung injury was induced by infusion of live Pseudomonas aeruginosa (5 x 10(8) CFU/ml at 0.3 ml/20 kg/min) for 60 min (Group Ps, n = 6). Control animals (Group C, n = 3) received a 60-min infusion of sterile 0.9% saline.

CD18 expression of circulating PMNs was measured by quantitative immunofluorescent flow cytometry. Plasma **TNF** activity was measured by L929 fibroblast cytolytic assay. Group Ps developed a significant neutropenia by 30 min (14.9 +/- 2.5 vs 23.4 +/- 3.3 x 10(3) cells/microliter at baseline, P less than 0.05, ANOVA) with circulating neutrophils exhibiting significantly increased CD18 expression by 60 min (6.34 +/- 0.72 vs 5.01 +/- 0.52 equivalent **soluble** fluorescence molecules (ESFM) x 10(3) at baseline, P less than 0.05, ANOVA). Group Ps demonstrated a significant increase in plasma **TNF** activity by 30 min (2.5 +/- 0.9 vs 0.7 +/- 0.3 U/ml at baseline). There was no significant change in PMN count, PMN CD18 expression, or plasma **TNF** activity in Group C. In complimentary in vitro studies, porcine PMNs stimulated with recombinant human **TNF** -alpha (n = 5) demonstrated a time- and dose-dependent increase in CD18 expression.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

07688415 91207415
T2 open reading frame from the Shope fibroma virus encodes a **soluble** form of the **TNF** **receptor**.
Smith CA; Davis T; Wignall JM; Din WS; Farrah T; Upton C; McFadden G; Goodwin RG
Immunex Corporation, Seattle, WA 98101.
Biochem Biophys Res Commun (UNITED STATES) Apr 15 1991, 176 (1) p335-42, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A transcriptionally active open reading frame (T2) from Shope Fibroma Virus was recently shown to have striking sequence homology with members of a new superfamily of cell surface proteins, including a **receptor** for human **tumor** **necrosis** **factor**. Here we report that recombinant T2 protein expressed in COS cells is a **soluble**, secreted glycoprotein which specifically binds human **TNF** alpha and beta, and inhibits binding of these cytokines to native **TNF** **receptors** on cells. T2 binding of **TNF** is not inhibited by nerve growth factor, although the nerve growth factor **receptor** is also a member of the same family, nor by nine other recombinant cytokines. Further, the repeating domain structure of T2 most closely resembles that of the type I **TNF** **receptor** (p75) and is significantly different from other family members, including the type II **TNF** **receptor** (p55). Since T2 possesses a leader sequence but lacks a transmembrane domain, these results confirm the original suggestion (1) that T2 represents a **soluble** form of the type I **TNF** **receptor** which is secreted from virally infected cells, and whose function is to immunosuppress the host by abrogating the potentially destructive effects of **TNF**. This is the first such virally-encoded **soluble** cytokine **receptor** to be identified, and may represent a more general mechanism by which viruses subvert the host immune system.

3/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

07665719 91184719
IgA triggers **tumor** **necrosis** **factor** alpha secretion by monocytes: a study in normal subjects and patients with alcoholic cirrhosis.
Deviere J; Vaerman JP; Content J; Denys C; Schandene L; Vandenbussche P; Sibille Y; Dupont E
Department of Gastroenterology, Hopital Erasme, Universite Libre de Bruxelles, Belgium.
Hepatology (UNITED STATES) Apr 1991, 13 (4) p670-5, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Under endotoxin-free conditions, peripheral blood mononuclear cells and purified monocytes isolated from healthy control subjects and patients with alcoholic cirrhosis disclose elevated **tumor** **necrosis** **factor**

alpha messenger RNA level and produce **tumor** **necrosis** **factor** alpha in response to stimulation by either **soluble** polymeric IgA or monomeric IgA bound to the surface of culture dishes but not by **soluble** monomeric IgA. Polymeric IgA induces **tumor** **necrosis** **factor** alpha secretion in a dose-dependent fashion. These results suggest that cross-linking of Fc alpha **receptors** on human monocytes induces the messenger RNA accumulation and the secretion of the cytotoxic and immunoregulatory cytokine **tumor** **necrosis** **factor** alpha. Furthermore, it is shown that lipopolysaccharide-induced **tumor** **necrosis** **factor** alpha secretion by peripheral blood mononuclear cells is synergistically enhanced in the presence of solid phase monomeric IgA but not in the presence of either **soluble** monomeric or polymeric IgA. Although increased lipopolysaccharide-induced **tumor** **necrosis** **factor** alpha secretion is observed at baseline in alcoholic cirrhotic patients, this synergism is also expressed in this group of patients. These observations could be of pathophysiological relevance in alcoholic cirrhosis because monomeric IgA deposits along the liver sinusoids and increased serum levels of polymeric IgA are common even in the early stages of this disease.

3/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

07645709 91164709
Interleukin-2, **soluble** interleukin-2 **receptor** and **tumor** **necrosis** **factor** in sera from patients with rheumatoid arthritis.
Corvetta A; Luchetti MM; Pomponio G; Della Bitta R; Recchioni A; Strusi P ; De Sio G; Danieli G
Istituto di Clinica Medica Generale e Terapia Medica, Universita degli Studi di Ancona.
Ric Clin Lab (ITALY) Oct-Dec 1990, 20 (4) p275-81, ISSN 0390-5748
Journal Code: TEA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Interleukin-2 (IL-2), **soluble** interleukin-2 **receptor** (IL-2R) and **tumor** **necrosis** **factor** (**TNF**) have been measured in sera from 47 patients affected by classic rheumatoid arthritis (RA) using an enzyme-linked immunosorbent assay. The patients were divided into 4 groups as follows: group A, 18 patients with inactive disease; group B, 19 patients with active disease under treatment with non-steroidal antiinflammatory drugs (NSAID) and second-line drugs; group C, 5 patients with active disease under treatment with NSAID and cyclosporine A (CSA) for at least 4 months; group D, 5 patients in the same condition as patients of group C, but treated with azathioprine (AZA) instead of CSA. IL-2 was undetectable in all patients except two, both characterized by active disease. **Soluble** IL-2R levels were above the upper limit of the normal range in most of the patients studied, but the mean value (+/- 1 SD) was significantly higher in patients of group B (1,288 +/- 421 U/ml) than in patients of group A (686 +/- 205 U/ml) and group C (842 +/- 414 U/ml). In two patients affected by active RA treated with pulse methylprednisolone therapy (1 g/day for 3 alternate days) the values of **soluble** IL-2R dropped from 948 to 662 U/ml and from 660 to 518 U/ml, respectively. No statistically significant correlation was observed between the serum level of IL-2R and the RF titre or percentage of C1q-binding activity, respectively. **TNF** was found within the normal range in all patients except one, who was characterized by active arthritis, high number of rheumatoid skin nodules and extremely high RF titre.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/30
DIALOG(R)File 155:MEDLINE(R)

07636428 91155428
Serum interleukin-2 (IL-2), **soluble** IL-2 **receptors** and **tumor** **necrosis** **factor** -alfa levels are significantly increased in acute myeloid leukemia patients.
Cimino G; Amadori S; Cava MC; De Sanctis V; Petti MC; Di Gregorio AO; Sgadari C; Vegna L; Cimino G; Mandelli F

Hematology, Department of Human Biopathology, University La Sapienza, Rome, Italy.
Leukemia (ENGLAND) Jan 1991, 5 (1) p32-5, ISSN 0887-6924
Journal Code: LEU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serum interleukin-2 (IL-2), **soluble** IL-2 **receptors** (sIL-2R) and **tumor** **necrosis** **factor**-alfa (**TNF** -alpha) levels were determined in 66 previously untreated consecutive patients with acute myeloid leukemia (AML) and in 22 normal volunteers. The following mean (+/- SE) values were observed in patients and controls, respectively: 35 +/- 14.7 (range 0.5-500) and 0.7 +/- 0.02 (0.5-0.8 U/ml for IL-2 (p = 0.001); 1622 +/- 289 (110-10,600) and 422 +/- 30 (207-666) U/ml for sIL-2R (p = 0.0001); 1247 +/- 196 (218-4672) and 152 +/- 11 (75-308) pg/ml for **TNF** -alpha (p = 0.0001). With respect to the FAB classification system, we found a significantly different distribution of serum IL-2 mean values in distinct subcategories, i.e. 3.4 +/- 1.9 U/ml in M1-M2-M3 and 42.4 +/- 20.4 U/ml in M4-M5 subgroups, respectively (p = 0.01), whereas sIL-2R and **TNF** -alpha levels were 1144 +/- 322 U/ml and 1120 +/- 317 pg/ml in M1-M2-M3 patients and 1945 +/- 317 U/ml and 1270 +/- 259 pg/ml in the M4-M5 group. A significantly positive correlation between **TNF**-alpha and sIL-2R (r = 0.53; p = 0.002) was also detected in the M4-M5 group. Sixty-three out of 66 patients received an intensive chemotherapy program. Univariate analysis showed that age and sIL-2R greater than 2000 U/ml significantly affected both complete remission rate and overall survival, whereas by multivariate analysis, age was the only independent variable significantly influencing survival. These data confirm recent in vitro evidence suggesting the role of IL-2, sIL-2R, and **TNF**-alpha in the control of normal hematopoiesis and leukemogenesis. Since the availability of recombinant cytokines for clinical use in AML, it is crucial to understand their spectrum of interaction in order to select the appropriate combination for in vivo administration.

3/3,AB/31
DIALOG(R)File 155:MEDLINE(R)

07634900 91153900
Effect of azidothymidine (AZT) on HIV P24 antigen, beta 2-microglobulin, neopterin, **soluble** CD8, **soluble** interleukin-2 **receptor** and **tumor** **necrosis** **factor** alpha levels in patients with AIDS-related complex or AIDS.
Reddy MM; McKinley G; Englard A; Grieco MH
R. A. Cooke Institute of Allergy, St Luke's-Roosevelt Hospital Center New York, New York 10019.
Int J Immunopharmacol (ENGLAND) 1990, 12 (7) p737-41, ISSN 0192-0561
Journal Code: GRI
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE; MULTICENTER STUDY
Circulating HIV P24 antigen, beta 2-microglobulin, neopterin, **soluble** CD8, **soluble** interleukin-2 **receptor** and **TNF** alpha levels were measured in 20 patients (9 with ARC and 11 with AIDS) treated with azidothymidine (AZT) and in 12 patients (3 with ARC and 9 with AIDS) who were in a placebo group. Mean levels of HIV P24 antigen, beta 2-microglobulin, neopterin and SCD8 decreased significantly (P less than 0.05) after 12 to 16 weeks of AZT administration. SIL-2R and **TNF** alpha serum levels did not appear to change in association with AZT therapy. No changes were observed in the placebo group except that **TNF** alpha levels appeared to increase after 12 to 16 weeks. These results suggest that AZT administration may have led to reduced HIV P24 antigen, beta 2-microglobulin, neopterin and SCD8 mean levels in these patients.

3/3,AB/32
DIALOG(R)File 155:MEDLINE(R)

07586865 91105865
The principal **tumor** **necrosis** **factor** **receptor** in monocyte cytotoxicity is on the effector cell, not on the target cell.
Peck R; Brockhaus M; Frey JR

F. Hoffmann-LaRoche Ltd., Basel, Switzerland.
Cell Immunol (UNITED STATES) Feb 1991, 132 (2) p308-18, ISSN 0008-8749 Journal Code: CQ9
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Several tumor target cell lines, prototypically K562 cells, are resistant to lysis by recombinant **tumor** **necrosis** **factor** (**TNF** alpha) but are killed by monocytes expressing membrane-associated **TNF**, suggesting that membrane **TNF** could account for monocyte-mediated cytotoxicity. Formaldehyde-fixed monocytes or extracted monocyte membrane fragments are cytotoxic to K562 target cells. Treatment of monocytes with interferon-gamma (IFN-gamma) increases cytotoxicity by live and fixed cells or by extracted monocyte membranes. Both **TNF** and **TNF** **receptors** are detectable on monocyte membranes by FACS analysis, and the levels of each are modulated by treatment with IFN-gamma. Cytotoxicity can be inhibited by either anti-**TNF** or anti-**TNF** **receptor** antibodies. Incubation of effector cells with exogenous **soluble** **TNF** prior to fixation or membrane preparation increases their cytotoxicity. In contrast, incubation of the target cells with exogenous **TNF** neither increases nor decreases killing by effector cell membrane fragments or intact effector cells. The data suggest that the **TNF** **receptors** on the effector cell, but not on the target cell, play a crucial role in **TNF**-mediated cytotoxicity.

3/3,AB/33
DIALOG(R)File 155:MEDLINE(R)

07572539 91091539
Increased levels of **soluble** interleukin-2 **receptors** and **tumor** **necrosis** **factor** in serum of patients with myelodysplastic syndromes [letter] [see comments]
Zoumbos N; Symeonidis A; Kourakli A; Katevas P; Matsouka P; Perraki M; Georgoulias V
Blood (UNITED STATES) Jan 15 1991, 77 (2) p413-4, ISSN 0006-4971 Journal Code: A8G
Comment in Blood 1991 Jun 15;77(12):2795-6
Languages: ENGLISH
Document type: LETTER

3/3,AB/34
DIALOG(R)File 155:MEDLINE(R)

07571841 91090841
Molecular cloning and expression of human and rat **tumor** **necrosis** **factor** **receptor** chain (p60) and its **soluble** derivative, **tumor** **necrosis** **factor**-binding protein.
Himmler A; Maurer-Fogy I; Kronke M; Scheurich P; Pfizenmaier K; Lantz M; Olsson I; Hauptmann R; Stratowa C; Adolf GR
Ernst Boehringer Institut, Bender + Co GesmbH, Vienna, Austria.
DNA Cell Biol (UNITED STATES) Dec 1990, 9 (10) p705-15, ISSN 1044-5498 Journal Code: AF9
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factor**-alpha (**TNF** -alpha), a protein released by activated macrophages, is involved in a wide variety of human diseases including septic shock, cachexia, and chronic inflammation. **TNF** binding protein (**TNF**-BP), a glycoprotein with high affinity to **TNF**-alpha isolated from urine, acts as an inhibitor of **TNF**-alpha by competing with the cell-surface **TNF** **receptor**. We report here the partial amino acid sequencing of human **TNF**-BP as well as the isolation, sequence, and expression of cDNA clones encoding a human and rat **TNF** **receptor**. The calculated Mr of the mature human and rat **TNF** **receptor** chains is 47,526 and 48,072, respectively. The extracellular ligand binding domain represents the **soluble** **TNF** -BP which is released by proteolytic cleavage. **TNF**-BP contains 24 cysteine residues and three potential N-glycosylation sites and shows sequence homology to the extracellular portions of **TNF**-R p80 chain and nerve growth factor **receptor**. Transfection of the human **TNF** **receptor** cDNA into

mammalian cells resulted in increased binding capacity for **TNF**-alpha and increased reactivity with a monoclonal antibody directed against the human **TNF** **receptor** chain p60. When a stop codon was introduced into the cDNA at the site corresponding to the carboxyl terminus of **TNF**-BP, transfected cells secreted a protein that reacted with antibodies raised against natural **TNF**-BP.

3/3,AB/35
DIALOG(R)File 155:MEDLINE(R)

07569061 91088061
Serum and CSF levels of IL-2, sIL-2R, **TNF**-alpha, and IL-1 beta in chronic progressive multiple sclerosis: expected lack of clinical utility.
Peter JB; Boctor FN; Tourtellotte WW
Specialty Laboratories, Santa Monica, CA 90404-3900.
Neurology (UNITED STATES) Jan 1991, 41 (1) p121-3, ISSN 0028-3878 Journal Code: NZO
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We measured interleukin-2 (IL-2), **soluble** IL-2 **receptor** (sIL-2R), **tumor** **necrosis** **factor**-alpha (**TNF**-alpha), and interleukin-1 beta (IL-1 beta) by ELISA in paired sera and CSF from 50 chronic progressive multiple sclerosis (CPMS) patients during worsening disability, 19 patients with other neurologic diseases (OND), and in sera from 40 healthy volunteers. In the CPMS patients, 28% (14/50), 10% (5/50), 16% (8/50), and 6% (3/50) had elevated serum levels of IL-2, sIL-2R, **TNF** -alpha and IL-1 beta, respectively, compared with healthy controls. The only analyte we detected in the CSF was IL-2 in 1 CPMS patient (1/50, 2%). We also saw elevated serum sIL-2R in 16% (3/19) of OND patients. We found no significant difference in mean levels of serum sIL-2R between the 3 groups. Our study, the largest to date of CPMS patients, shows that serum and CSF levels of IL-2, sIL-2R, **TNF** -alpha, or IL-1 beta are not sensitive for, and the serum sIL-2R level is not specific for, CPMS. Therefore, measurement of these analytes will not be clinically useful for therapeutic or prognostic purposes in the majority of CPMS patients.

3/3,AB/36
DIALOG(R)File 155:MEDLINE(R)

07543364 91062364
Purification and characterization of an inhibitor (**soluble** **tumor** **necrosis** **factor** **receptor**) for **tumor** **necrosis** **factor** and lymphotoxin obtained from the serum ultrafiltrates of human cancer patients.
Gatanaga T; Hwang CD; Kohr W; Cappuccini F; Lucci JA 3d; Jeffes EW; Lentz R; Tomich J; Yamamoto RS; Granger GA
Department of Molecular Biology and Biochemistry, University of California, Irvine 92717.
Proc Natl Acad Sci U S A (UNITED STATES) Nov 1990, 87 (22) p8781-4, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Serum ultrafiltrates (SUF) from human patients with different types of cancer contain a blocking factor (BF) that inhibits the cytolytic activity of human **tumor** **necrosis** **factor** alpha (**TNF**-alpha) in vitro. BF is a protein with a molecular mass of 28 kDa on reducing sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS/PAGE). The active material was purified to homogeneity by a combination of affinity chromatography, PAGE, and high-pressure liquid chromatography. Amino acid sequence analysis revealed that BF is derived from the membrane **TNF** **receptor**. Purified BF blocks the lytic activity of recombinant human and mouse **TNF** -alpha and recombinant human lymphotoxin on murine L929 cells in vitro. However, BF inhibits the lytic activity of **TNF**-alpha more effectively than it does that of lymphotoxin. The BF also inhibits the necrotizing activity of recombinant human **TNF**-alpha when coinjected into established cutaneous Meth A tumors in BALB/c mice. The BF may have an important role in (i) the regulation and control of **TNF**-alpha and lymphotoxin activity in cancer patients, (ii) interaction between the tumor

and the host antitumor mechanisms, and (iii) use of systemically administered **TNF**-alpha in clinical trials with human cancer patients.

3/3,AB/37
DIALOG(R)File 155:MEDLINE(R)

07537135 91056135
Characterization in vitro of a human **tumor** **necrosis** **factor** -binding protein. A **soluble** form of a **tumor** **necrosis** **factor** **receptor**.
Lantz M; Gullberg U; Nilsson E; Olsson I
Department of Medicine, University of Lund, Sweden.
J Clin Invest (UNITED STATES) Nov 1990, 86 (5) p1396-42, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tumor **necrosis** **factor** (**TNF**) is a pleiotropic mediator of inflammatory responses. A cysteine-rich, highly glycosylated 30-kD **TNF** -binding protein (**TNF** -BP) purified from urine may have a role in regulation because it protects in vitro against the biological effects of **TNF**. The cytotoxic effect of **TNF** on the fibrosarcoma cell line WEHI 164 was inhibited by 50% at a 10-fold excess of **TNF**-BP. The binding of **TNF** to the **receptor** was partially reversed after the addition of **TNF** -BP. Results from biosynthetic labeling of cells with 35S-cysteine followed by immunoprecipitation with anti-**TNF**-BP indicated that **TNF** -BP is formed and released at the cell surface by cleavage because no corresponding cellular polypeptide was observed. A cellular 60-kD polypeptide, which was immunoprecipitated with anti-**TNF** -BP, may correspond to the transmembrane **TNF**-**receptor** molecule and be the precursor of **TNF**-BP. Thus, **TNF**-BP appears to be a **soluble** form of a transmembrane **TNF**-**receptor**. Moreover our results demonstrate that the production of **TNF**-BP is increased when the **TNF** **receptor** is downregulated in cells by treatment with **TNF** or by activation of protein kinase C with phorbol esters. **TNF**-BP may be an important agent that blocks harmful effects of **TNF**, and, therefore, useful in clinical applications.

3/3,AB/38
DIALOG(R)File 155:MEDLINE(R)

07526991 91045991
A second **tumor** **necrosis** **factor** **receptor** gene product can shed a naturally occurring **tumor** **necrosis** **factor** inhibitor.
Kohno T; Brewer MT; Baker SL; Schwartz PE; King MW; Hale KK; Squires CH; Thompson RC; Vannice JL
Synergen, Inc., Boulder, CO 80301.
Proc Natl Acad Sci U S A (UNITED STATES) Nov 1990, 87 (21) p8331-5, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
An inhibitor of **tumor** **necrosis** **factor** (**TNF**) has been isolated from the human histiocytic lymphoma cell line U-937 that is capable of inhibiting both **TNF**-alpha and **TNF** -beta. Protein sequencing has verified that it is distinct from a previously described **TNF** inhibitor that is a **soluble** fragment of a **TNF** **receptor** molecule (**TNFrI**). The cDNA sequence of this second **TNF** inhibitor clone suggests that it is also a **soluble** fragment of a **TNF** **receptor**. Expression of this cDNA sequence in COS-7 cells verified that it encodes a **receptor** for **TNF**-alpha (**TNFrII**) that can give rise to a **soluble** inhibitor of **TNF**-alpha, presumably through proteolytic cleavage. The extracellular domain of **TNFrII** has significant homology with that of **TNFrI** and these two **receptors** share a striking conservation of cysteine residue alignment with the extracellular domain of the nerve growth factor **receptor**. These three **receptor** molecules are therefore members of a family of polypeptide hormone **receptors**.

3/3,AB/39

DIALOG(R)File 155:MEDLINE(R)

07498509 91017509
Cloning of human **tumor** **necrosis** **factor** (**TNF**) **receptor** cDNA and expression of recombinant **soluble** **TNF**-binding protein.
Gray PW; Barrett K; Chantry D; Turner M; Feldmann M
Charing Cross Sunley Research Centre, Hammersmith, London, England.
Proc Natl Acad Sci U S A (UNITED STATES) Oct 1990, 87 (19) p7380-4, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The cDNA for one of the **receptors** for human **tumor** **necrosis** **factor** (**TNF**) has been isolated. This cDNA encodes a protein of 455 amino acids that is divided into an extracellular domain of 171 residues and a cytoplasmic domain of 221 residues. The extracellular domain has been engineered for expression in mammalian cells, and this recombinant derivative binds **TNF** alpha with high affinity and inhibits its cytotoxic activity in vitro. The **TNF** **receptor** exhibits similarity with a family of cell surface proteins that includes the nerve growth factor **receptor**, the human B-cell surface antigen CD40, and the rat T-cell surface antigen OX40. The **TNF** **receptor** contains four cysteine-rich subdomains in the extracellular portion. Mammalian cells transfected with the entire **TNF** **receptor** cDNA bind radiolabeled **TNF** alpha with an affinity of 2.5 x 10(-9) M. This binding can be competitively inhibited with unlabeled **TNF** alpha or lymphotoxin (**TNF** beta).

3/3,AB/40
DIALOG(R)File 155:MEDLINE(R)

07493450 91012450
TNF, **soluble** IL-2R and **soluble** CD-8 in Behcet's disease [letter]
Akoglu TF; Direskeneli H; Yazici H; Lawrence R
J Rheumatol (CANADA) Aug 1990, 17 (8) p1107-8, ISSN 0315-162X Journal Code: JWX
Languages: ENGLISH
Document type: LETTER

3/3,AB/41
DIALOG(R)File 155:MEDLINE(R)

07487021 91006021
Soluble forms of **tumor** **necrosis** **factor** **receptors** (**TNF**-Rs). The cDNA for the type I **TNF**-R, cloned using amino acid sequence data of its **soluble** form, encodes both the cell surface and a **soluble** form of the **receptor**.
Nophar Y; Kemper O; Brakebusch C; Englemann H; Zwang R; Aderka D; Holtmann H; Wallach D
Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.
EMBO J (ENGLAND) Oct 1990, 9 (10) p3269-78, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Two proteins which specifically bind **tumor** **necrosis** **factor** (**TNF**) have recently been isolated from human urine in our laboratory. The two proteins cross-react immunologically with two species of cell surface **TNF** **receptors** (**TNF**-R). Antibodies against one of the two **TNF** binding proteins (TBPI) were found to have effects characteristic of **TNF**, including stimulating phosphorylation of specific cellular proteins. Oligonucleotide probes designed on the basis of the NH2-terminal amino acid sequence of TBPI were used to clone the cDNA for the structurally related cell surface type 1 **TNF**-R. It is notable that although this **receptor** can signal the phosphorylation of cellular proteins, it appears from its amino acid sequence to be devoid of intrinsic protein kinase activity. The extracellular domain of the **receptor** is

composed of four internal cysteine-rich repeats, homologous to structures repeated four times in the extracellular domains of the nerve growth factor **receptor** and the B lymphocytes surface antigen CDw40. The amino acid composition and size of the extracellular domain of the type I **TNF**-R closely resemble those of TBPI. The COOH-terminal amino acid sequence of the four cysteine rich repeats within the extracellular domain of the type I **TNF** -R matches the COOH-terminal sequence of TBPI. Amino acid sequences in the extracellular domain also fully match other sequences found in TBPI. On the other hand, amino acid sequences in the **soluble** form of the type II **TNF**-R (TBPII), while indicating a marked homology of structure, did not suggest any identity between this protein and the extracellular domain of the type I **TNF**-R. CHO cells transfected with type I **TNF**-R cDNA produced both cell surface and **soluble** forms of the **receptor**. The **receptor** produced by CHO cells was recognized by several monoclonal antibodies against TBPI, reacting with several distinct epitopes in this molecule. These data suggest that the **soluble** forms of the **TNF** -Rs are structurally identical to the extracellular cytokine binding domains of these **receptors** and are consistent with the notion that the **soluble** forms are, at least partly, derived from the same transcripts that encode the cell surface **receptors**.

3/3,AB/42
DIALOG(R)File 155:MEDLINE(R)

07470055 90377055
Bone resorption and cytokines: the role of IL-1 beta, **TNF** and lymphotoxin]
Riassorbimento osseo e citochine: ruolo della IL-1 beta, del **TNF** e della linfotossina.
Piattelli A; Trisi P; D'Addona A
Cattedra di Patologia Speciale Odontostomatologica, Universita degli Studi G. D'Annunzio, Chieti.
Minerva Stomatol (ITALY) Jun 1990, 39 (6) p447-51, ISSN 0926-4970 Journal Code: NB2
Languages: ITALIAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English Abstract
Tumor **necrosis** **factor** (**TNF**) and interleukin-1 (IL-1) are **soluble** factors that play a pivotal role in acute and chronic inflammation. **TNF** is a 17 Kda protein mainly released by monocytes and macrophages and is a common mediator of toxic shock, cachexia and tumor necrosis. IL-1 was first described as a lymphocyte activating factor and it was then discovered that IL-1 has a number of other biological activities and that there are at least two major types of IL-1 (alpha and beta) which bind to the same **receptor**. Recently it has been shown that **TNF** and IL-1 beta have an important role in bone resorption.

3/3,AB/43
DIALOG(R)File 155:MEDLINE(R)

07454968 90361968
Tumoricidal effector mechanisms of murine BCG-activated macrophages: role of **TNF** in conjugation-dependent and conjugation-independent pathways.
Klostergaard J; Stoltje PA; Kull FC Jr
Department of Tumor Biology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
J Leukoc Biol (UNITED STATES) Sep 1990, 48 (3) p220-8, ISSN 0741-5400 Journal Code: IWY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The roles of secreted and membrane-associated **TNFs** were investigated in activated macrophage cytolysis of L929, EMT-6, and P815 targets. While all three targets were susceptible to cytolysis in coculture, an anti-**TNF** antiserum blocked lysis of L929 and EMT-6 but not of the P815 targets. Of the three targets, recombinant human or mouse **TNF** could only lyse the L929 target; despite the fact that a role for **TNF** was invoked in lysis of EMT-6 targets in coculture, the latter was strongly resistant to **soluble** rTNF, even at concentrations 30-40-fold higher

than the Ka for its **TNF**-**receptor**. Cytolysis of the L929 target occurred when it was cocultured with BCG-activated macrophages even when these effector cells did not secrete **TNF**, either due to prior chemical crosslinking or to lack of exposure to a triggering level of lipopolysaccharide. Furthermore, by introduction of the anti-**TNF** antiserum over a dose-range, it was shown that macrophage cytolysis both of L929 and EMT-6 targets occurred in the absence of bioavailable, fluid-phase **TNF**. Thus, even for targets susceptible to fluid-phase **TNF**, **TNF** -dependent, direct macrophage-mediated cytolysis appears to be a function independent of secreted **TNF** and one that utilizes effector-target contact to express the action of a membrane form of the molecule.

3/3,AB/44
DIALOG(R)File 155:MEDLINE(R)

07450606 90357606
Soluble interleukin-2 **receptor** (sIL-2R) and **tumor** **necrosis** **factor** plasma levels in renal allograft recipients.
Noronha IL; Daniel V; Rambausek M; Waldherr R; Opelz G
Department of Transplantation Immunology, University of Heidelberg, FRG.
Transplant Proc (UNITED STATES) Aug 1990, 22 (4) p1859-60, ISSN 0041-1345 Journal Code: WE9
Languages: ENGLISH
Document type: JOURNAL ARTICLE

3/3,AB/45
DIALOG(R)File 155:MEDLINE(R)

07447443 90354443
Antibodies to a **soluble** form of a **tumor** **necrosis** **factor** (**TNF**) **receptor** have **TNF**-like activity.
Engelmann H; Holtmann H; Brakebusch C; Avni YS; Sarov I; Nophar Y; Hadas E; Leitner O; Wallach D
Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.
J Biol Chem (UNITED STATES) Aug 25 1990, 265 (24) p14497-504, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Immunological cross-reactivity between **tumor** **necrosis** **factor** (**TNF**) binding proteins which are present in human urine (designated TBPI and TBPII) and two molecular species of the cell surface **receptors** for **TNF** is demonstrated. The two **TNF** **receptors** are shown to be immunologically distinct, to differ in molecular weight (58,000 and 73,000), and to be expressed differentially in different cells. It is further shown that polyclonal antibodies against one of the **TNF** binding proteins (TBPI) display, by virtue of their ability to bind the **TNF** **receptor**, activities which are very similar to those of **TNF**. These antibodies are cytotoxic to cells which are sensitive to **TNF** toxicity, induce resistance to **TNF** toxicity, enhance the incorporation of thymidine into normal fibroblasts, inhibit the growth of chlamydiae, and induce the synthesis of prostaglandin E2. Monovalent F(ab) fragments of the polyclonal antibodies lack **TNF**-like activities, but acquire them upon cross-linking with anti-F(ab)2 antibodies, suggesting that the ability of the anti-TBPI antibodies to mimic **TNF** correlates with their ability to cross-link the **TNF** **receptors**. This notion was further supported by data obtained in a comparative study of the **TNF**-like cytotoxicity of a panel of monoclonal antibodies against TBPI. The induction of **TNF**-like effects by antibodies to a **TNF** **receptor** suggests that **TNF** is not directly involved in intracellular signalling. Rather, it is the **receptors** to this cytokine which, when properly triggered in a process which appears to involve clustering of these **receptors**, transduce the signal for response to **TNF** into the cell's interior.

3/3,AB/46
DIALOG(R)File 155:MEDLINE(R)

07417880 90324880
Shedding of **tumor** **necrosis** **factor** **receptors** by activated human neutrophils.
Porteu F; Nathan C
Department of Medicine, Cornell University Medical College, New York, New York 10021.
J Exp Med (UNITED STATES) Aug 1 1990, 172 (2) p599-607, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The capacity of human neutrophils (PMN) to bind **tumor** **necrosis** **factor** (**TNF**) was rapidly lost when the cells were incubated in suspension with agents that can stimulate their migratory and secretory responses. Both physiological (poly)peptides (FMLP, C5a, CSF-GM) and pharmacologic agonists (PMN, calcium ionophore A23187) induced the loss of **TNF** **receptors** (**TNF**-R) from the cell surface. Half-maximal loss in **TNF**-R ensued after only approximately 2 min with 10(-7) M FMLP at 37 degrees C, and required only 10(-9) M FMLP during a 30-min exposure. However, there were no such changes even with prolonged exposure of PMN to FMLP at 4 degrees or 16 degrees C. Scatchard analysis revealed loss of **TNF** -binding sites without change in their affinity (Kd approximately 0.4 nM) as measured at incompletely modulating concentrations of FMLP, C5a, PMA, or A23187. The binding of anti-**TNF**-R mAbs to PMN decreased in parallel, providing independent evidence for the loss of **TNF**-R from the cell surface. At the same time, **soluble** **TNF**-R appeared in the medium of stimulated PMN. This inference was based on the PMN- and FMLP-dependent generation of a nonsedimentable activity that could inhibit the binding of **TNF** to fresh human PMN or to mouse macrophages, and the ability of mAbs specific for human **TNF**-R to abolish inhibition by PMN-conditioned medium of binding of **TNF** to mouse macrophages. **Soluble** **TNF** -R activity was associated with a protein of Mr approximately 28,000 by ligand blot analysis of cell-free supernatants of FMLP-treated PMN. Thus, some portion of the FMLP-induced loss of **TNF**-R from human PMN is due to shedding of **TNF**-R. Shedding was unaffected by inhibitors of serine and thiol proteases and could not be induced with phosphatidylinositol-specific phospholipase C. Loss of **TNF**-R from PMN first stimulated by other agents may decrease their responsiveness to **TNF**. **TNF**-R shed by PMN may be one source of the **TNF**-binding proteins found in body fluids, and may blunt the actions of the cytokine on other cells.

3/3,AB/47
DIALOG(R)File 155:MEDLINE(R)

07404367 90311367
Characterization of a **tumor** **necrosis** **factor** alpha (**TNF** -alpha) inhibitor: evidence of immunological cross-reactivity with the **TNF** **receptor**.
Seckinger P; Zhang JH; Hauptmann B; Dayer JM
Department of Medicine, Hopital Cantonal Universitaire, Geneva, Switzerland.
Proc Natl Acad Sci U S A (UNITED STATES) Jul 1990, 87 (13) p5188-92, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous studies have shown that urine of febrile patients contains a **tumor** **necrosis** **factor** alpha inhibiting activity (**TNF**-alpha Inh) when tested in a cytotoxicity assay using the **tumor** **necrosis** **factor** alpha (**TNF**-alpha)-susceptible cell line L929. In the present study, we investigated the relationship between the **TNF**-alpha Inh and a potential **soluble** form of the **receptor**, as the former has been shown to block **TNF** -alpha activities by binding to the ligand. We demonstrate that human **TNF**-alpha is affected to a greater extent than is murine **TNF** -alpha. This species specificity of the inhibitor correlates with the binding studies of **TNF** **receptor** interactions already reported. We raised a polyclonal antibody to **TNF**-alpha Inh that neutralizes its activity and does not recognize **TNF**-alpha. Solubilized cross-linked 125I-labeled **TNF**-alpha **receptor** complex could be immunoprecipitated by using either anti-**TNF**-alpha or anti-**TNF**-alpha

Inh antibody, suggesting immunological cross-reactivity between the **receptor** and the inhibitor. By using fluorescein isothiocyanate-coupled **TNF** -alpha, it was possible to visualize by fluorescence-activated cell sorter analysis the **TNF**-alpha **receptor** on phytohemagglutinin/interl eukin 2-activated T cells. A similar increase of immunofluorescence intensity of the activated T cells was observed by using anti-**TNF**-alpha Inh antibody revealed with a fluorescein isothiocyanate-coupled goat anti-rabbit IgG1 conjugate, suggesting that the **TNF**-alpha Inh is also expressed as a membrane protein. Taken together, our results suggest that the **TNF**-alpha Inh originally described might be a **soluble** form of the **TNF** **receptor** itself.

3/3,AB/48
DIALOG(R)File 155:MEDLINE(R)

07384731 90291731
Serum levels of **tumor** **necrosis** **factor**, interleukin 2 **receptor** , and interferon-gamma in Kawasaki disease involved coronary-artery lesions.
Matsubara T; Furukawa S; Yabuta K
Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan.
Clin Immunol Immunopathol (UNITED STATES) Jul 1990, 56 (1) p29-36, ISSN 0090-1229 Journal Code: DEA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We investigated 45 patients with Kawasaki disease (KD) and report the first simultaneous determination of **tumor** **necrosis** **factor** (**TNF**), interleukin 2 **receptor** (IL-2R) and interferon-gamma (IFN-gamma) in the serum during acute phase. Serum levels of **TNF** were measured by a sandwich enzyme-linked immunosorbent assay. Serum levels of **soluble** IL-2R and IFN-gamma were measured by a sandwich enzyme immunoassay and radioimmunoassay, respectively. Serum levels of **TNF**, IL-2R, and IFN-gamma were seen to increase during the acute phase of KD. In KD patients with coronary-artery lesions (CAL), the percentage of positive cases for **TNF** (greater than or equal to 10 U/ml), IL-2R (greater than or equal to 1056 U/ml), and IFN-gamma (greater than or equal to 0.3 U/ml) was higher than that in patients without CAL. Our results suggest that aggressive activation of immunocompetent cells develops in KD with CAL.

3/3,AB/49
DIALOG(R)File 155:MEDLINE(R)

07328285 90235285
Molecular cloning and expression of a **receptor** for human **tumor** **necrosis** **factor**.
Schall TJ; Lewis M; Koller KJ; Lee A; Rice GC; Wong GH; Gatanaga T; Granger GA; Lentz R; Raab H; et al
Department of Molecular Biology, Genentech, Inc., South San Francisco, California 94080.
Cell (UNITED STATES) Apr 20 1990, 61 (2) p361-70, ISSN 0092-8674 Journal Code: CQ4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A human **tumor** **necrosis** **factor** (**TNF**) binding protein from serum of cancer patients was purified to homogeneity and partially sequenced. Synthetic DNA probes based on amino acid sequence information were used to isolate cDNA clones encoding a **receptor** for **TNF**. The **TNF** **receptor** (**TNF** -R) is a 415 amino acid polypeptide with a single membrane-spanning region. The extracellular cysteine-rich domain of the **TNF**-R is homologous to the nerve growth factor **receptor** and the B cell activation protein Bp50. Human embryonic kidney cells transfected with a **TNF**-R expression vector specifically bind both 125I-labeled and biotinylated **TNF**-alpha. Unlabeled **TNF**-alpha and **TNF**-beta were equally effective at displacing the binding of labeled **TNF**-alpha to **TNF**-R expressing cells. Northern analysis indicates a single species of mRNA for the **TNF**-R in a variety of cell types. Therefore, the **soluble** **TNF** binding protein found in human serum is probably

proteolytically derived from the **TNF**-R.

3/3,AB/50
DIALOG(R)File 155:MEDLINE(R)

07292919 90199919
TPA induction of EL4 resistance to macrophage-released **TNF**: role of ADP-ribosylation in tumoricidal activities of **TNF** and other factors.
Fishman M; Essani N; Costlow M
Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101-0318.
Cell Immunol (UNITED STATES) Apr 15 1990, 127 (1) p78-91, ISSN 0008-8749 Journal Code: CQ9
Contract/Grant No.: CA 18672, CA, NCI; P30 CA 21765, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activated macrophages synthesize and release numerous tumoricidal **soluble** factors that can be divided into **receptor** - or nonreceptor-dependent agents. **Tumor** **necrosis** **factor** (**TNF**) would be an example of the former. In our experimental model the killing of EL4 thymoma cells by syngeneic activated macrophages involves, but not exclusively, **TNF**. Our results show that approximately 50% of the anti-EL4 activity expressed by macrophages can be specifically inhibited with rabbit anti-mouse **TNF** antibody. EL4 variants resistant to the lytic activity of **TNF** were still susceptible to macrophage-mediated lysis. A tumor-promoting phorbol ester, TPA, rendered **TNF**-sensitive and -insensitive EL4 cells resistant to M phi-mediated lysis. However, TPA down-regulated **TNF**-specific binding sites on both **TNF**-sensitive and -resistant cell surface membranes, suggesting that resistance to **TNF** involves postligand:**receptor** events. Tumor cell G-protein involvement (ADP-ribosylation), as a result of **TNF**-**TNF** **receptor** interactions, was investigated. The results showed that pertussis toxin was cytotoxic against **TNF** -sensitive and -resistant EL4 cells but not against TPA-treated target cells. Inhibitors of ADP-ribosyltransferase inhibited pertussis toxin cytotoxicity and macrophage-mediated lysis but did not interfere with recombinant **TNF** lytic activity.

3/3,AB/51
DIALOG(R)File 155:MEDLINE(R)

07279029 90186029
Plasma elastase-alpha 1-antitrypsin, neopterin, **tumor** **necrosis** **factor**, and **soluble** interleukin-2 **receptor** after prolonged exercise.
Dufaux B; Order U
Institut fur Kreislaufforschung und Sportmedizin, Deutsche Sporthochschule Koln, FRG.
Int J Sports Med (GERMANY, WEST) Dec 1989, 10 (6) p434-8, ISSN 0172-4622 Journal Code: GRK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effects of a 2.5-h running test on the plasma concentrations of elastase-alpha 1-antitrypsin, neopterin, **tumor** **necrosis** **factor**, and **soluble** interleukin-2 **receptor** were evaluated in eight healthy young male subjects. Neopterin was measured by radioimmunoassay, elastase-alpha 1-antitrypsin, **tumor** **necrosis** **factor**, and **soluble** interleukin-2 **receptor** by enzyme immunoassay. The post-exercise values were corrected for plasma volume changes which were calculated from hematocrit and hemoglobin values. Compared with the concentrations before exercise, elastase-alpha 1-antitrypsin values were significantly increased during the run (1 h after the start) (P less than 0.01) as well as during the first few hours after the end of the running test (P less than 0.01). A significant increase of **tumor** **necrosis** **factor** and neopterin was observed 1 h after the end and 1,3, and 24 h after the end of the running test, respectively, (P less than 0.01), and **soluble** interleukin-2 **receptor** concentrations were significantly elevated 1 and 2 days after exercise (P less than 0.01). The increase of elastase-alpha 1-antitrypsin, neopterin, **tumor** **necrosis** **factor**,

and **soluble** interleukin-2 **receptor** supports the concept of a functional involvement of polymorphonuclear neutrophils and an activation of macrophages and T-lymphocytes after prolonged exercise.

3/3,AB/52
DIALOG(R)File 155:MEDLINE(R)

07247802 90154802
Cross-linking of both Fc gamma RI and Fc gamma RII induces secretion of **tumor** **necrosis** **factor** by human monocytes, requiring high affinity Fc-Fc gamma R interactions. Functional activation of Fc gamma RII by treatment with proteases or neuraminidase.
Debets JM; Van de Winkel JG; Ceuppens JL; Dieteren IE; Buurman WA
Department of Surgery, University of Limburg, Maastricht, The Netherlands.
J Immunol (UNITED STATES) Feb 15 1990, 144 (4) p1304-10, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cross-linking of Fc gamma R on human monocytes with human IgG has been shown to induce secretion of the inflammatory and immunoregulatory cytokine **TNF** . In the present study we examined the role of both constitutively expressed monocyte Fc gamma R, the 72-kDa high affinity Fc gamma R (Fc gamma RI), and the 40-kDa low affinity **receptor** (Fc gamma RII), in the induction of **TNF** secretion. On the basis of preferential binding of the Fc moiety of murine mAb of different isotype, Fc gamma RI and Fc gamma RII were selectively cross-linked by using either solid-phase murine (m)IgG2a, or solid-phase mIgG1, respectively. On freshly isolated, untreated monocytes only cross-linking of Fc gamma RI with solid-phase mIgG2a induced **TNF** secretion. The interaction between Fc gamma RII and mIgG1 could be enhanced by treatment of monocytes with proteases or with the desialylating enzyme neuraminidase. After treatment of monocytes with these enzymes, **TNF** secretion was effectively induced by solid-phase mIgG1, apparently through cross-linking of Fc gamma RII. However, mIgG1-induced **TNF** secretion differed between protease-treated monocytes from high responder individuals and monocytes from low responder individuals, **TNF** secretion being considerably less in the latter population. Protease-treated monocytes and mononuclear cells from individuals with an inherited defect in cell membrane expression of Fc gamma RI were induced to secrete **TNF** by solid-phase human IgG, confirming the capacity of Fc gamma RII to induce **TNF** secretion. It was not possible to induce **TNF** secretion by cross-linking Fc gamma RI or Fc gamma RII with anti-Fc gamma R mAb and **soluble** or solid-phase anti-mIgG, indicating that high affinity Fc-Fc gamma R interactions are necessary to induce release of this cytokine.

3/3,AB/53
DIALOG(R)File 155:MEDLINE(R)

07203215 90110215
Two **tumor** **necrosis** **factor** -binding proteins purified from human urine. Evidence for immunological cross-reactivity with cell surface **tumor** **necrosis** **factor** **receptors**.
Engelmann H; Novick D; Wallach D
Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.
J Biol Chem (UNITED STATES) Jan 25 1990, 265 (3) p1531-6, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Two proteins which specifically bind **tumor** **necrosis** **factor** (**TNF**) were isolated from human urine by ligand (**TNF**)-affinity purification, followed by reversed phase high performance liquid chromatography. The molecular weights of the two proteins, as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, were similar (about 30,000). Both proteins provided protection against the cytocidal effect of **TNF** in vitro and both bound **TNF**-alpha more effectively than **TNF** -beta. Antibodies raised against each of the proteins had an inhibitory effect on the binding of **TNF** to cells, suggesting that both

proteins are structurally related to the **TNF** **receptors**. However, the two proteins differed in NH2-terminal amino acid sequences: Asp-Ser-Val-Cys-Pro- in one and Val-Ala-Phe-Thr-Pro- in the other. The NH2-terminal sequence of the former protein was invariable, while that of the latter was truncated to varying degrees. The two proteins were also immunologically distinct. The relative efficacy of anti-sera against the two proteins in inhibiting the binding of **TNF** to cells varied markedly from one line of cells to another. Evidence has been presented recently for the existence of two distinct molecular species of cell surface **receptors** for **TNF** and for differential expression of those two **receptors** by cells of different lines. The findings presented in this study are consistent with the notion that the urinary **TNF**-binding proteins constitute **soluble** forms of the two molecular species of the cell surface **TNF** **receptors**.

3/3,AB/54
DIALOG(R)File 155:MEDLINE(R)

07080786 89382786
Interleukin-1 and **tumor** **necrosis** **factor** alpha can be induced from mononuclear phagocytes by human immunodeficiency virus type 1 binding to the CD4 **receptor**.
Merrill JE; Koyanagi Y; Chen IS
Department of Neurology, Jonsson Comprehensive Cancer Center, Los Angeles, California.
J Virol (UNITED STATES) Oct 1989, 63 (10) p4404-8, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: RO-1 NS26983; NS 25508
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cytokines such as interleukin-1 (IL-1) and **tumor** **necrosis** **factor** alpha (**TNF** alpha) are important in normal immune processes. In this study, we demonstrate that human immunodeficiency virus type 1 (HIV-1) virions induce normal peripheral blood mononuclear phagocytes to produce both IL-1 and **TNF** within a few hours after their exposure to virus. The induction of these cytokines by HIV-1 does not require a productive infection. Blocking studies with **soluble** CD4 indicate that the effect is mediated through the CD4 molecule. In addition, the treatment of mononuclear phagocytes with OKT4A monoclonal antibody mimics the effects of HIV-1. Thus, these results indicate that induction of IL-1 and **TNF** alpha can occur via signals mediated through the CD4 molecule on mononuclear phagocytes. **TNF** has been shown by other investigators to induce HIV-1 expression. Therefore, **TNF** alpha may play a role in autocrine and paracrine regulation of HIV-1 expression. In addition, the induction of IL-1 and **TNF** by HIV-1 may also contribute to some of the neurologic and physiologic disorders associated with acquired immunodeficiency syndrome.

3/3,AB/55
DIALOG(R)File 155:MEDLINE(R)

07057254 89359254
Multimeric structure of the **tumor** **necrosis** **factor** **receptor** of HeLa cells.
Smith RA; Baglioni C
Department of Biological Sciences, State University of New York, Albany 12222.
J Biol Chem (UNITED STATES) Sep 5 1989, 264 (25) p14646-52, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA29895
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The **tumor** **necrosis** **factor** (**TNF**) **receptor** of HeLa cells was solubilized in Triton X-100 and characterized by gel filtration, affinity labeling, and ligand blotting studies. **Receptors** solubilized with Triton X-100 eluted in gel filtration as a major peak of Mr = 330,000 and retained high affinity binding (KD = 0.25 nM). Affinity labeling of **soluble** **receptor**/125I-**TNF** complexes using the reversible,

bifunctional bis[2-(succinimidooxycarbonyl-oxy)ethyl] sulfone resulted in the formation of cross-linked species of Mr = 310,000, 150,000-175,000, 95,000, and 75,000. The formation of these complexes was competitively inhibited by unlabeled **TNF**. Partial reversal of cross-linking in these complexes and their analysis by two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) resolved 125I-**TNF** dimers cleaved from the 95,000 band and 125I-**TNF** monomer cleaved from the 75,000 band, providing evidence for a Mr approximately 60,000 subunit. In addition, the 95,000 and 75,000 bands were resolved as components of larger complexes (Mr = 150,000-175,000), which presumably contain two **receptor** subunits. The Mr 95,000 and 75,000 bands were also released from the Mr 310,000 complex by reduction with dithiothreitol, suggesting a role for disulfide bond stabilization. To investigate the association of the putative **receptor** subunits, Triton X-100 extracts from HeLa membranes were fractionated by SDS-PAGE without reduction and transferred electrophoretically to nylon membranes for **TNF** binding assays. Only two bands of Mr = 60,000 and 70,000 specifically bound **TNF**, and higher Mr binding activity was not observed. These results indicate that **TNF**. **receptors** in HeLa cells are high molecular weight complexes containing Mr = 60,000 and 70,000 subunits each capable of binding **TNF** and that the complexes are primarily stabilized by non-covalent, hydrophobic interactions.

3/3,AB/56
DIALOG(R)File 155:MEDLINE(R)

07042016 89344016
Natural cytotoxic activity in a cloned natural killer cell line is mediated by **tumor** **necrosis** **factor**.
Richards AL; Dennert G; Pluznik DH; Takagaki Y; Djeu JY
Department of Medical Microbiology and Immunology, University of South Florida, College of Medicine, Tampa.
Nat Immun Cell Growth Regul (SWITZERLAND) 1989, 8 (2) p76-88, ISSN 0254-7600 Journal Code: NIC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The interleukin-2-dependent mouse natural killer (NK) cell line NKB61A2 concomitantly exhibits NK and natural cytotoxic (NC) activities. This was determined by the cells' ability to lyse both the NK-sensitive YAC-1 lymphoma and the NC-sensitive WEHI-164 fibrosarcoma cell lines in a 4- and 18-hour 51Cr release assay, respectively. Cell-free supernatant from NKB61A2 cells grown in culture for 48 h had substantial lytic activity against WEHI-164. The mouse mast cell line PT18-A17 and the rat basophilic leukemia cell line RBL-2H3, which both express NC activity, also produced a **soluble** factor during culture which lysed WEHI-164 cells. This activity was increased in the basophilic/mast cells by crossbridging the surface IgE **receptors** . Similar results were obtained by triggering the basophilic NC cells with the calcium ionophore ionomycin and the tumor promoter phorbol-12-myristate-13-acetate (PMA). Such triggering of NKB61A2 cells, however, did not significantly increase their NC activity. Interestingly, both ionomycin and PMA had an inhibitory effect on the NK activity of NKB61A2. Recently it has been found that **tumor** **necrosis** **factor** (**TNF**) is a major mediator of NC activity. To determine if the **soluble** factor responsible for the NC activity of the NK clone was related to **TNF**, a rabbit polyclonal antiserum to mouse **TNF** was tested against the cell-free culture medium of NKB61A2, PT18-A17, RBL-2H3 and murine recombinant **TNF** (Mu-rTNF). The lytic activity of the culture medium from all these cells and the Mu-rTNF control was abrogated by this antibody. These data suggest that the murine cell line NKB61A2 has both NK and NC activities and that the NC activity is due to a factor immunologically similar to **TNF** . In addition, the enhancement of NC activity in the NK cell line is apparently under control by a separate pathway, different from that in the basophilic cells.

3/3,AB/57
DIALOG(R)File 155:MEDLINE(R)

06859892 89161892

Recombinant **tumour** **necrosis** **factor** (**TNF**) fixed to cell monolayers retains its cytotoxic and growth-stimulatory activity. Evidence that internalization of **TNF** is not necessary for induction of biological effects.

Hofsli E; Nissen-Meyer J

Institute of Cancer Research, University of Trondheim, Norway.

Scand J Immunol (ENGLAND) Jan 1989, 29 (1) p57-63, ISSN 0300-9475 Journal Code: UCW

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Recombinant human **tumour** **necrosis** **factor** (rTNF) retained its cytotoxic activity after being fixed with paraformaldehyde to adherent cell monolayers. The cytotoxicity appeared to be mainly due to fixed rTNF and not to any free **soluble** rTNF that could have leaked out from the fixed rTNF cell preparations. The fixed rTNF cell preparations also stimulated the growth of human diploid fibroblasts, under conditions where little growth-stimulatory activity was found in suspension. These results indicate that **TNF** may exert its effect on target cells without internalization, perhaps through a **receptor**-mediated process that may alter the levels of a second messenger within the target cells. This signal transduction does not appear to involve cAMP or cGMP, since we were unable to detect significant changes in the levels of these two second messengers in **TNF** -exposed WEHI 164 clone 13 cells.

3/3,AB/58

DIALOG(R)File 155:MEDLINE(R)

06858854 89160854

Cell lines cultured at high density are resistant to lysis by **tumor** **necrosis** **factor** and natural cytotoxic cells.

Patek PQ; Lin Y; Case PG

Salk Institute, Developmental Biology Laboratory, San Diego, California 92138.

Proc Soc Exp Biol Med (UNITED STATES) Mar 1989, 190 (3) p234-9, ISSN 0037-9727 Journal Code: PXZ

Contract/Grant No.: CA34805

Languages: ENGLISH

Document type: JOURNAL ARTICLE

It has been suggested that natural cytotoxic (NC) cell activity and **tumor** **necrosis** **factor** (**TNF**), the molecular mediator of NC activity, are capable of protecting individuals against the progression of incipient tumors or could be useful in cancer therapy regimens. Much of this speculation arises as a result of in vitro studies, on a variety of tumor cells, demonstrating the cytolytic and cytostatic properties of NC and **TNF** activities. Here, evidence is presented showing that certain mouse fibroblast cell lines, generally considered sensitive to NC and **TNF** lysis, are quite resistant to these lytic activities when cultured at high cell density. Although a **soluble** factor that renders these same target cells resistant to NC and **TNF** lysis has been described, no such factor is involved in this high density-induced resistance. Rather, it appears that cell to cell contact of the targets is critical. Moreover, the induced resistance to NC and **TNF** lysis does not result from loss of either NC recognition determinants or **TNF** **receptors** by the target cells, but is the consequence of increased expression of a protein synthesis-dependent resistance mechanism. These observations raise the issue of the in vivo phenotype of cells characterized in vitro as sensitive to NC and **TNF** lysis. It is entirely possible that certain cells which are considered sensitive to NC and **TNF** activities are, in fact, resistant to these cytolytic activities when growing as tumors (i.e., at high cell density). Should this be the so, NC and **TNF** cytolytic activities may not function in vivo or may function only via some indirect means.

3/3,AB/59

DIALOG(R)File 155:MEDLINE(R)

06837454 89139454

Macrophages rapidly internalize their **tumor** **necrosis** **factor**

receptors in response to bacterial lipopolysaccharide.
Ding AH; Sanchez E; Srimal S; Nathan CF
Beatrice and Samuel A. Seaver Laboratory, Department of Medicine, Cornell University Medical College, New York 10021.
J Biol Chem (UNITED STATES) Mar 5 1989, 264 (7) p3924-9, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA43610
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effect of bacterial lipopolysaccharide (LPS) on macrophage **receptors** for **tumor** **necrosis** **factor**/cachectin (**TNF**-R) was studied. At equilibrium, iodinated recombinant human **TNF** alpha (rTNF alpha) bound to 1100 +/- 200 sites/cell on macrophage-like RAW 264.7 cells with a Kd of 1.3 +/- 0.1 x 10(-9) M. Preexposure of RAW 264.7 cells to 10 ng/ml LPS for 1 h at 37 degrees C resulted in complete loss of cell surface **TNF** alpha binding sites. 50% loss ensued after 1 h with 0.6 ng/ml LPS, or after 15 min with 10 ng/ml LPS. Complete loss of **TNF** alpha binding sites occurred without change in numbers of complement **receptor** type 3. No decrease in **TNF**-R followed preexposure to LPS at 4 degrees C, nor could LPS displace 125I-rTNF alpha from its binding sites. Although **TNF** -R disappeared from the surface of intact macrophages following exposure to LPS, specific **TNF** alpha binding sites were unchanged in permeabilized macrophages, indicating that **TNF**-R were rapidly internalized. Conditioned media from LPS-treated RAW 264.7 cells induced 30% down-regulation of **TNF** -R on macrophages from LPS-hyporesponsive mice (C3H/HeJ), suggesting that a **soluble** macrophage product may be responsible for a minor portion of the LPS effect. Additional evidence against endogenous **TNF** alpha being the major cause of **TNF**-R internalization was the rapid onset of the effect of LPS on **TNF**-R compared to the reported onset of **TNF** alpha production, the relatively high concentrations of exogenous rTNF alpha required to mimic the effect of LPS, and the inability of **TNF** alpha-neutralizing antibody to block the effect of LPS. LPS-induced down-regulation of **TNF**-R was complete or nearly complete not only in RAW 264.7 cells, but also in primary macrophages of both human and murine origin, was less marked in human endothelial cells, and was absent in human granulocytes and melanoma cells and mouse L929 cells. Thus, in situ, macrophages and some other host cells may be resistant to the actions of **TNF** alpha produced during endotoxinemia, because such cells may internalize their **TNF**-R in response to LPS before **TNF** alpha is produced.

3/3,AB/60
DIALOG(R)File 155:MEDLINE(R)

06707853 89009853
Natural cytotoxic cell-specific cytotoxic factor produced by IL-3-dependent basophilic/mast cells. Relationship to **TNF**.
Richards AL; Okuno T; Takagaki Y; Djeu JY
Department of Medical Microbiology/Immunology, University of South Florida, Tampa 33612.
J Immunol (UNITED STATES) Nov 1 1988, 141 (9) p3061-6, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The murine IL-3-dependent mast cell line, PT18-A17, and the rat basophilic leukemia cell line, RBL-2H3, were found to mediate natural cytotoxic (NC) activity via the release of a **soluble** factor which specifically lysed NC-sensitive WEHI-164 but not NK-sensitive YAC-1 tumor cells. The release of this NC cell-specific cytotoxic factor was enhanced by triggering of both types of cells via IgE **receptor** bridging. This factor had activity on **TNF**-sensitive but not **TNF**-resistant cell lines and could be neutralized by two independently produced polyclonal anti-mouse **TNF** antisera. It was not neutralized by antibodies against mouse IFN-alpha/beta or IFN-gamma. Moreover, it was not neutralized by a monoclonal or a polyclonal anti-human **TNF** , demonstrating that the rodent **TNF** differed antigenically from human **TNF**. These results indicate that the cytotoxic factor released from a murine IL-3-dependent mast cell line and from a rat basophilic leukemia cell line is immunologically and functionally related to murine **TNF**.

3/3,AB/61
DIALOG(R)File 155:MEDLINE(R)

06640729 88285729
Fc-**receptor** cross-linking induces rapid secretion of **tumor** **necrosis** **factor** (cachectin) by human peripheral blood monocytes.
Debets JM; Van der Linden CJ; Dieteren IE; Leeuwenberg JF; Buurman WA
Department of General Surgery, University of Limburg, Maastricht, The Netherlands.
J Immunol (UNITED STATES) Aug 15 1988, 141 (4) p1197-201, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this study it was demonstrated that cross-linking of FcR on human monocytes induces the secretion of the cytotoxic and immunoregulatory cytokine **TNF**. Both **soluble** and insoluble immune complexes, solid-phase antibody and antibody-coated phagocytizable particles were used to cross-link FcR on monocytes. It was observed that monocytes secreted large amounts of **TNF** in each of these instances. Kinetic studies performed with **soluble** immune complexes showed that **TNF** was secreted very rapidly, e.g., within 2 h after addition of immune complexes to monocytes. These findings are relevant for the understanding of FcR-mediated immune responses by monocytes and macrophages, for example antibody-dependent cellular cytotoxicity and phagocytosis, and for disease states associated with circulating or tissue-fixed immune complexes.

3/3,AB/62
DIALOG(R)File 155:MEDLINE(R)

06389404 88034404
Immune regulation of the L5178Y murine tumor-dormant state. II. Interferon-gamma requires **tumor** **necrosis** **factor** to restrain tumor cell growth in peritoneal cell cultures from tumor-dormant mice.
Suzuki Y; Liu CM; Chen LP; Ben-Nathan D; Wheelock EF
Department of Pathology and Laboratory Medicine, Hahnemann University, Philadelphia, PA 19102.
J Immunol (UNITED STATES) Nov 1 1987, 139 (9) p3146-52, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: CA32577
Languages: ENGLISH
Document type: JOURNAL ARTICLE
L5178Y lymphoma cells are restrained from progressive growth in peritoneal cell ("in vitro tumor-regressor" PC) cultures prepared from many DBA/2 mice which harbor the tumor cells in the peritoneal cavity in a tumor-dormant state. Treatment of these PC cultures with 'antibodies to murine interferon-gamma (MuIFN-gamma) and murine **tumor** **necrosis** **factor** (MuTNF) but not with antibody to interleukin 2 (IL-2) **receptors** eliminated the restraint on tumor cell growth and permitted their progressive proliferation. L5178Y cells were found to be resistant to the direct toxic effects of large concentrations (3,000 U/ml) of MuIFN-gamma and of MuTNF, either alone or in combination. Treatment of PC cultures from tumor-dormant mice, in which tumor cells grew progressively ("in vitro tumor-progressor"), but not PC cultures from normal mice, with exogenous MuIFN-gamma resulted in a marked inhibition of tumor cell growth. The MuIFN-gamma-induced cytotoxic activity was cell-mediated since no **soluble** tumor-cytotoxic factors could be detected in the cultures. MuIFN-gamma induced cytotoxic activity in plastic-adherent peritoneal cell (AD-PC) cultures, but induced no cytotoxic activity in nonadherent-PC cultures unless small numbers (2%) of AD-PC were present, and inclusion of antibody to MuTNF in these mixed PC cultures blocked the development of cytotoxic activity. Antibody to MuTNF also blocked the development of cytotoxic activity in cultures of MuIFN-gamma-treated whole PC and AD-PC from tumor-dormant mice. These results indicate that MuIFN-gamma and MuTNF are both important in restraining tumor cell growth in PC cultures from tumor-dormant mice, and that MuIFN-gamma requires the presence of MuTNF to induce cytotoxic activity in these cultures.

3/3,AB/63
DIALOG(R)File 155:MEDLINE(R)

06307632 87281632
Down regulation of the **receptors** for **tumor** **necrosis** **factor** by interleukin 1 and 4 beta-phorbol-12-myristate-13-acetate.
Holtmann H; Wallach D
J Immunol (UNITED STATES) Aug 15 1987, 139 (4) p1161-7, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Binding of radiolabeled **tumor** **necrosis** **factor** (**TNF**) to cell surface **receptors** was markedly reduced in human foreskin fibroblasts and cells from SV-80 and HeLa cell lines subsequent to treatment with interleukin 1 (IL-1) or 4 beta-phorbol-12-myristate-13-aceta te (PMA). The decrease in **TNF** binding was initiated within minutes of application of IL-1 or PMA and could not be blocked by cycloheximide, suggesting that it is independent of protein synthesis. Scatchard plot analysis of **TNF** binding to the SV-80 cells indicated that its decrease in response to IL-1 and PMA reflects a reduced amount of **TNF** **receptors** , with no change in their affinity. IL-1 and PMA together had an additive effect on **TNF** binding. Treatment with **TNF** did not result in decreased binding of IL-1 to its **receptors** nor did **TNF** and IL-1 compete directly for their respective **receptors**. Human U937 cells on which **receptors** for IL-1 were below detectable levels exhibited no decrease in **TNF** binding when treated with IL-1, but did so in response to PMA. In addition to a decrease in **TNF** **receptors**, cells treated with IL-1 or PMA exhibited a lesser vulnerability to the cytolytic effect of **TNF**. The two kinds of changes were not completely correlated. A particularly notable dissimilarity was evident when comparing the rate of their reversal: the **TNF** **receptor** level was fully recovered within a few hours of removal of IL-1 or of the water-**soluble** analogue of PMA, 4 beta-phorbol-12,13-dibutyrate, from pretreated SV-80 cells; yet at that time resistance to the cytotoxicity of **TNF** was still prominent. These findings indicate that IL-1 as well as tumor-promoting phorbol diesters can down regulate cellular response to **TNF** by inducing a decrease in the number of **receptors** for **TNF**, and apparently through some other effect(s) as well.

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DIALOG(R)File 155:MEDLINE(R)

06083114 87057114
Binding and crosslinking of 125I-labeled recombinant human **tumor** **necrosis** **factor** to cell surface **receptors**.
Yoshie O; Tada K; Ishida N
J Biochem (Tokyo) (JAPAN) Sep 1986, 100 (3) p531-41, ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Highly purified recombinant human **tumor** **necrosis** **factor** (**TNF**) (molecular mass determined as 17 kilodaltons (kDa) by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and as 36 kDa by Sephadex G-100 gel chromatography) was labeled with 125I to a specific activity of 5 microCi/micrograms without appreciable loss of activity. The binding of 125I-**TNF** to eighteen human and twelve animal cell lines was examined. The binding varied considerably among different cell lines. In most cell lines, the binding was inhibited up to greater than 90% by the addition of a 100-fold excess of unlabeled **TNF**. Some human and mouse cell lines showed no significant binding above background levels, suggesting that these cell lines had no **receptors** for **TNF**. Among the **TNF** **receptor** -positive cell lines, there was no direct correlation between the level of specific **TNF** binding and the level of sensitivity to the cytotoxic or cytostatic effect of **TNF**. Some cell lines were sensitive to **TNF**, whereas others were not affected at all by **TNF**. The **TNF** **receptor**-negative cell lines were also resistant to **TNF**. Therefore, although the existence of **TNF** **receptor** seems to be necessary, it does not alone determine cellular sensitivity to **TNF**. Scatchard analysis of the binding data revealed that human HeLa S3

and THP-1 had about 50,000 and 10,000 **receptors** /cell with a dissociation constant (KD) of 0.3-0.5 nM, respectively. Similarly, mouse L-929 and L-M cells had about 5,000 **receptors**/cell with KD of 3-5 nM. 125I-**TNF** bound to HeLa S3 cells was rapidly internalized at 37 degrees C, presumably by **receptor**-mediated endocytosis, and degraded to acid-**soluble** products. The turnover of **TNF** **receptors** on HeLA S3 cells seemed to be rapid, since the level of specific binding quickly decreased after treatment with 100 micrograms/ml of cycloheximide at 37 degrees C with a half-life of about 1.5 h. The crosslinking of the cell-bound 125I-**TNF** with the use of disuccinimidyl suberate yielded a complex of 105 kDa for HeLa S3 and THP-1 cells, and a complex of 100 kDa for U937 cells. The crosslinking was completely inhibited by the addition of a 100-fold excess of unlabeled **TNF**. Assuming that the complex was due to a one-to-one association of the dimeric form of **TNF** (34 kDa) with the **receptor**, we estimated the molecular size of the human **TNF** **receptor** to be 71 kDa for HeLa S3 and THP-1, and 66 kDa for U937.

3/3,AB/65
DIALOG(R)File 155:MEDLINE(R)

05766958 86067958
Tumor **necrosis** **factor**: specific binding and internalization in sensitive and resistant cells.
Tsujimoto M; Yip YK; Vilcek J
Proc Natl Acad Sci U S A (UNITED STATES) Nov 1985, 82 (22) p7626-30, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: AI12948; AI07057; CA37385
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Highly purified, Escherichia coli-derived recombinant human **tumor** **necrosis** **factor** (**TNF**) was labeled with 125I and employed to determine **receptor** binding, internalization, and intracellular degradation in murine L929 cells (highly sensitive to the cytotoxic action of **TNF**) and in diploid human FS-4 cells (resistant to **TNF** cytotoxicity). 125I-labeled **TNF** bound specifically to high-affinity **receptors** on both L929 and FS-4 cells. Scatchard analysis of the binding data indicated the presence of 2200 binding sites per L929 cell and 7500 binding sites per FS-4 cell. The calculated dissociation constants are 6.1 X 10(-10) M and 3.2 X 10(-10) M for L929 and FS-4 cells, respectively. In both L929 and FS-4 cells, incubation at 37 degrees C resulted in a rapid internalization of the bulk of the cell-bound **TNF**, followed by the appearance of trichloroacetic acid-**soluble** 125I radioactivity in the tissue culture medium, due to degradation of **TNF**. Degradation but not cellular uptake of **TNF** was inhibited in the presence of chloroquine (an inhibitor of lysosomal proteases) in both L929 and FS-4 cells, suggesting that degradation occurs intracellularly, probably within lysosomes. These results show that resistance of FS-4 cells to **TNF** cytotoxicity is not due to a lack of **receptors** or their inability to internalize and degrade **TNF**.

3/3,AB/66
DIALOG(R)File 155:MEDLINE(R)

05732787 86033787
Binding of human **tumor** **necrosis** **factor** to high affinity **receptors** on HeLa and lymphoblastoid cells sensitive to growth inhibition.
Baglioni C; McCandless S; Tavernier J; Fiers W
J Biol Chem (UNITED STATES) Nov 5 1985, 260 (25) p13395-7, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA29895; AI20429
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Purified human **tumor** **necrosis** **factor** (**TNF**) was iodinated to high specific activity with good retention of its biological activity, as determined by the cytotoxic titer on murine L929 cells. The binding of 125I-**TNF** to L929 and human HeLa S2 cells grown in monolayer was initially measured, but high levels of nonspecific binding were observed.

Specific binding to high affinity **receptors** of HeLa S2 cells grown in suspension culture was demonstrated by competitive displacement experiments and analysis of the binding data with the LIGAND program. A KD of 2 X 10(-10) M and 6000 **receptors**/cell were calculated in this way. These observations provide the first direct evidence for a cellular **receptor** for **TNF**. The cell-bound 125I-**TNF** was internalized at 37 degrees C, presumably by **receptor**-mediated endocytosis, and subsequently degraded to acid-**soluble** products. Three lines of human lymphoblastoid cells were examined for sensitivity to the cytostatic effect of **TNF** and for the presence of high affinity **receptors**. Daudi and Raji cells were insensitive to **TNF** and showed very few specific binding sites when incubated with 125I-**TNF**. Jurkat cells were growth-inhibited by **TNF** and showed a significantly greater number of specific binding sites than the other lymphoblastoid cells. These findings suggest that the sensitivity of some cell lines to the biological effects of **TNF** may be correlated with the presence of a relatively high number of **receptors** for this factor.